Medicaid Dossier for *Coreg CR*

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1. EXECUTIVE SUMMARY

Indications

Coreg CR (carvedilol phosphate) Extended-Release Capsule is indicated for the treatment of mild to severe heart failure (HF), post-myocardial infarction left ventricular dysfunction (post-MI LVD), and essential hypertension.

Heart Failure (mild to severe)

Coreg CR is indicated for the treatment of mild to severe HF of ischemic or cardiomyopathic origin, usually in addition to diuretics, angiotensin-converting enzyme (ACE) inhibitors, and digitalis, to increase survival and also to reduce the risk of hospitalization in patients with mild to severe HF. The heart failure indication for *Coreg CR* is based on data demonstrating the pharmacokinetic and predicted pharmacodynamic equivalence of *Coreg* and *Coreg CR* across dosage strengths in patients with mild, moderate, and severe HF.(1)

- Four pivotal clinical trials from the U.S. Carvedilol HF Trials (USCHFT) Program evaluated the use of *Coreg* in patients with primarily mild to moderate HF. In these trials, when compared to placebo, 6.5 months (mean) of *Coreg* added to conventional HF medications resulted in the following: a 38% reduction in the combined risk of all-cause death or hospitalization for a cardiovascular reason ($P < 0.001$); a 27% reduction in the risk of hospitalizations for cardiovascular reason alone ($P = 0.036$); a 65% reduction in all-cause mortality (not a pre-specified endpoint) ($P < 0.001$); and an average increase in left ventricular ejection fraction (LVEF) by 2% with placebo compared to 8% with Coreg ($P < 0.0001$).(2)
- The indication for *Coreg* and *Coreg CR* in severe HF is based on the results of COPERNICUS (CarvedilOl ProspEctive RaNdomIzed CumUlative Survival Trial), a large, randomized, multicenter, double-blind trial evaluating patients with severe HF. The addition of *Coreg* for a mean of 10.4 months to conventional HF therapy resulted in a 35% reduction in all-cause mortality ($P = 0.0014$); a 24% reduction in death or hospitalization for any reason ($P < 0.001$); and a 31% reduction in death or hospitalization for HF ($P = 0.000004$). Similar results were observed in all subgroups examined. (3) (4)
- The Carvedilol Or Metoprolol European Trial (COMET) was a multicenter, double-blind, randomized trial designed to directly compare the effects of *Coreg* (n = 1511) and metoprolol tartrate (n = 1518) on morbidity and mortality in patients with moderate to severe HF receiving a diuretic and an ACE inhibitor. Following a mean duration of 58 months, therapy with *Coreg* (mean achieved daily dose 41.8 mg) compared to metoprolol tartrate (mean achieved daily dose 85 mg) significantly reduced the risk of all-cause mortality by 17% ($P = 0.0017$), which was similar in magnitude across all subgroups. No difference was demonstrated for the co-primary endpoint of all-cause mortality or all-cause hospitalization, however therapy with *Coreg* compared to metoprolol tartrate was associated with significant risk reductions in the following secondary endpoints: fatal or non-fatal myocardial infarction, cardiovascular mortality, death from stroke, sudden death, and new-onset diabetes-related adverse events. Patient-reported adverse events and withdrawal rates were similar between groups.(5)

Post-Myocardial Infarction Left Ventricular Dysfunction

Coreg CR is indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a MI and have a LVEF ≤ 40% (with or without symptoms of HF). The post-MI LVD indication for *Coreg CR* is based on data demonstrating the pharmacokinetic and predicted pharmacodynamic equivalence of *Coreg* and *Coreg CR* across dosage strengths in patients with asymptomatic or symptomatic post-MI LVD.(1)

- The CAPRICORN (CArvedilol Post-infaRct survIval COntRol in LV dysfuntioN) trial evaluated the effects of *Coreg* in patients post-MI with LVD (with or without symptoms of HF) in addition to modern post-MI therapy, including ACE inhibitors or angiotensin II receptor blockers, anticoagulants, lipid-lowering agents, diuretics, and aspirin. The mean duration of follow-up was 1.3 years. All-cause mortality was 12% with *Coreg* and 15% with placebo, representing a 23% risk reduction with *Coreg* ($P = 0.03$). Cardiovascular mortality was reduced by 25% ($P = .024$), and there was also a 40% reduction in fatal or non-fatal MI observed in the group treated with *Coreg* (*P*

= 0.01).[6] A meta-analysis of placebo-controlled trials of carvedilol in heart failure demonstrated similar reductions in the rate of reinfarction.[1]

Hypertension

Coreg CR is indicated for the management of essential hypertension, either alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.[1]

- In a double-blind, randomized, placebo-controlled 8-week trial, therapy with *Coreg CR* resulted in statistically significant reductions in blood pressure (BP) as measured by 24-hour ambulatory BP monitoring in 337 patients with essential hypertension. Placebo-subtracted mean changes from baseline in systolic/diastolic BP were -6.1/-4.0 mmHg, -9.4/-7.6 mmHg, -11.8/-9.2 mmHg for *Coreg CR* 20 mg, 40 mg, and 80 mg, respectively.[1]

special populations

- **Diabetes:** In a head-to-head trial comparing *Coreg* to metoprolol tartrate in patients with mild to moderate hypertension and type 2 diabetes, *Coreg* did not adversely affect glycemic control and improved insulin sensitivity relative to metoprolol tartrate.[7]
- **Diabetes:**A meta-analysis of 7 placebo-controlled randomized trials with *Coreg* in HF or post-MI LVD demonstrated similar survival benefit in patients with and without diabetes with a relative risk reduction of 28% ($P = 0.029$) and 37% ($P < 0.0001$), respectively. [8]
- **Race:** The benefits of *Coreg* in the USCHFT Program were apparent and of a similar magnitude in both black and nonblack patients with HF. [9]
- **Elderly:** Subgroup analyses in all pivotal HF and post-MI LVD trials for *Coreg*, found no overall difference in the safety or effectiveness of *Coreg*, between older and younger patients.[1] A prospective study involving 1,030 patients with HF greater than 70 years of age, found *Coreg* to be well-tolerated in 76% to 80% of patients with a mean dose achieved of 31.2 mg per day.[10]

Safety information

Patients taking *Coreg CR* should avoid abrupt cessation of therapy. Following abrupt cessation of therapy with certain β-blocking agents, exacerbation of angina pectoris and, in some cases, MI and ventricular arrhythmias have occurred. The dosage should be reduced gradually over a 1- to 2-week period and the patient should be carefully monitored. *Coreg CR* is contraindicated in patients with bronchial asthma or related bronchospastic conditions, second- or third-degree AV block, sick sinus syndrome or severe bradycardia (unless a permanent pacemaker is in place); in patients with cardiogenic shock or decompensated heart failure (HF) requiring the use of intravenous inotropic therapy (such patients should first be weaned from intravenous therapy before initiating *Coreg CR*); in patients with clinically manifest hepatic impairment; and in patients who are hypersensitive to any component of this product. Like other β-blockers, *Coreg CR* should be used with caution in patients with peripheral vascular disease, thyrotoxicosis, or who are undergoing major surgery. Caution should also be used in diabetic patients as β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Worsening heart failure or fluid retention may occur during uptitration of *Coreg CR*.

Differences in safety would not be expected based on the similarity in plasma levels for *Coreg CR* and *Coreg*. For *Coreg*, the most common side effects reported in the controlled trials in HF (reported in ≥10% of patients [both the mild-to-moderate and the severe populations studied] and more frequently on *Coreg*) were dizziness, fatigue, weight increase, hypotension, and bradycardia. Worsening HF symptoms were also reported, but with equal or greater frequency in placebo-treated patients. The most common side effects reported with *Coreg* in the CAPRICORN trial were consistent with the profile of the drug in the US HF trials and the COPERNICUS trial, as well as the health status of patients. The only additional adverse events reported in >3% of patients and more frequently on *Coreg* in CAPRICORN were dyspnea, lung edema, and anemia. The most common side effects in hypertension trials with carvedilol were nasopharyngitis (*Coreg CR*) and dizziness and fatigue (*Coreg*), which were generally mild.[1]

2. DISEASE DESCRIPTION

2.1 Disease Description for Heart Failure

- Epidemiology

Approximately five million Americans have heart failure, and about 550,000 new cases are diagnosed each year.[11] Heart failure mortality and hospitalization rates have steadily increased over the past two decades. Epidemiological studies indicate heart failure is the most common hospital discharge diagnosis in patients over the age of 65 and the fourth most common discharge diagnosis overall.[12,13] The estimated direct cost of heart failure management in the United States ranges from $25 to $38 billion annually with hospitalizations accounting for the majority of total direct cost.[11,14] Researchers estimate that 40% of all heart failure patients are hospitalized each year with a mean length of stay of seven days and an average total charge of $11,227 per visit.[15,16]

- Pathophysiology

Abnormal neurohormonal activation is a major contributor to heart failure disease progression.[17] The sympathetic nervous system (SNS) is activated early in the course of left ventricular dysfunction regardless of its cause (coronary artery disease [CAD], hypertension, etc.) to compensate for the failing heart and remains activated throughout the course of heart failure. However, this long term activation of the sympathetic nervous system leads to deleterious effects, such as chronic tachycardia and desensitization of beta-receptors in the myocardium, both of which undermine left ventricular function by further decreasing contractile strength. These adverse adaptations in the myocardium, kidneys, and peripheral vasculature lead to a progressive, paradoxical worsening of heart failure. Activation of the renin-angiotensin system (RAS) leads to increased peripheral vascular resistance as well as fluid and sodium retention, which contribute to the symptoms and progression of heart failure.

The myocardial dysfunction that results in heart failure can be classified as systolic, diastolic, or both. Systolic versus diastolic dysfunction is defined by an inability of the heart to pump sufficient blood (systolic dysfunction) or to fill normally (diastolic dysfunction).[17] The majority of patients with symptoms of heart failure have poor myocardial contractile performance, which is characterized as left ventricular systolic dysfunction (LVSD).[18] The principal hallmark of patients with LVSD is a depressed left ventricular ejection fraction (LVEF), generally less than 40%. Literature indicates that the majority (70%) of patients presenting with heart failure have reduced LVSD and variable degrees of diastolic dysfunction.[18,19]

- Risk Assessment and Clinical Presentation

Heart failure is a clinical syndrome characterized by symptoms of dyspnea and fatigue, which may limit exercise tolerance, and signs of fluid retention, which may lead to pulmonary congestion and peripheral edema.[18] The primary risk factors for developing HF include CAD, hypertension, valvular heart disease, damage to the heart from alcohol or other drugs and birth defects in the heart.[20]

The New York Heart Association (NYHA) classes can be used to quantify the degree of functional limitation imposed by heart failure.[18,21] This system assigns patients to one of four functional classes, depending on the degree of effort needed to elicit symptoms (Table 1). The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines have defined a new classification system to gauge the development and progression of heart failure (Table 2).[18]

Table 1. NYHA Functional Classification[18,21]

Class	Functional Capacity
I	Patients have cardiac disease with no limitations of physical activity. Ordinary activity does not produce any HF symptoms.
II	Patients have cardiac disease with slight limitations of physical activity. They have no symptoms at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea.
HF = heart failure	

Class	Functional Capacity
III	Patients have cardiac disease with marked limitations of physical activity. They have no symptoms at rest, but less than ordinary activity results in fatigue, palpitation, dyspnea.
IV	Patients have cardiac disease with an inability to carry on physical activity without discomfort. Symptoms are present at rest and any physical activity increases discomfort.
HF = heart failure	

- Treatment Options

Non-drug treatment options for heart failure primarily include lifestyle modifications including dietary/sodium restriction, alcohol avoidance, routine exercise, and smoking cessation.[18] Table 2 summarizes the recommended treatment approaches for heart failure based on the ACC/AHA heart failure guidelines. The recommendations reflect the ACC/AHA classification system of heart failure and consist of drug therapy initiation and lifestyle modification.

Table 2. ACC/AHA Heart Failure Stages and Recommended Therapy[18]

Stage/Description	Therapy
A Patients at high risk of developing HF secondary to comorbidities	Treat hypertension Treat lipid disorders Control metabolic syndrome Encourage lifestyle modifications (smoking cessation, regular exercise, discourage alcohol and illicit drug use) ACE inhibitor or ARB for appropriate patients
B Patients with structural heart disease without HF symptoms	All measures in Stage A ACE Inhibitor (or ARB) and beta-blocker for appropriate patients
C Patients with current or prior symptomatic HF and underlying structural damage	All measures in Stage A and B Sodium restriction Drugs for routine use include diuretic, ACE inhibitor, and beta-blocker Drugs for select patients include aldosterone antagonist, ARB, digitalis, hydralazine/nitrates Devices in select patients including biventricular pacing and implantable defibrillators
D Refractory HF requiring specialized interventions	All measures under Stages A, B, and C Decision: regarding appropriate level of care Options: compassionate end-of-life care/hospice or Extraordinary measures including mechanical assist devices, heart transplantation, chronic inotropes, experimental surgery or drugs
ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; HF = heart failure	

- Place of *Coreg CR* in Treatment

Several beta-blockers have been studied in patients with heart failure in controlled clinical trials[2,3,22,23,24,25,26] however, only *Coreg CR*, *Coreg*, and metoprolol succinate have been approved by the FDA for the treatment of heart failure. *Coreg CR* is indicated for the treatment of mild to severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival and, also, to reduce the risk of hospitalization.[1] Metoprolol succinate (TOPROL XL®) is indicated for the treatment of stable, symptomatic (NYHA class II or III) heart failure

of ischemic, hypertensive or cardiomyopathic origin.[27] Based on ACC/AHA Heart Failure guidelines, an evidence-based beta-blocker, such as carvedilol, should be considered as soon as LVD is diagnosed even if the patient does not yet present with heart failure symptoms and is recommended for use in patients with Stages B and C heart failure.[18] *Coreg CR* may also be used in patients with Stage A heart failure to treat pre-existing cardiovascular conditions such as hypertension, for which beta-blockers are first line therapy.

The use of once-daily *Coreg CR* may further improve patient care through improved adherence in patients with heart failure who require lifetime chronic therapy with multiple medications. Minimizing the total number of daily doses has been found to be more important in promoting adherence than minimizing the total number of medications.[28] A meta-analysis of 76 studies evaluating adherence using electronic monitoring devices identified an inverse relationship between the number of daily doses and the rate of adherence.[29] Studies using drugs dosed once daily had a mean compliance rate of 79% ± 14%, whereas studies measuring adherence with twice daily dosed drugs reported mean rates of 69% ± 15%. In patients with heart failure, investigators have reported that noncompliance with some aspect of the medical regimen ranges from 20% to 65%.[30] Additionally, nonadherence to therapy is one of the leading causes for worsening heart failure and has been shown to be a contributing factor in 20% to 64% of hospitalizations.

Despite national treatment guidelines and clinical trial evidence, beta-blockers are still significantly underused in patients with heart failure who do not have contraindications or documented intolerance.[31] Prescribers and payers should evaluate treatment regimens for their current patients with heart failure to assess compliance with nationally recognized guidelines. Increased utilization of guideline-recommended beta-blockers, such as carvedilol, can improve the health status of patients while reducing resource utilization and total costs for heart failure management.

2.2 Disease Description for LVD Following an MI

- Epidemiology

Coronary heart disease (CHD) is the single largest killer of men and women in America. In the year 2006 it is estimated that 700,000 Americans will have a new coronary attack and about 500,000 will have a recurrent attack.[11] In 2000, the development of a new or recurrent MI was estimated to have occurred in 1.1 million Americans with 40% of these cases being fatal.

[32] After having an initial recognized MI, 25% of men and 38% of women will die within 1 year. Left ventricular dysfunction, anterior wall infarction and complex ventricular ectopy associated with the event carry the highest one-year mortality post myocardial infarction.[33] Depending on variables such as sex and clinical outcome, people who are post-myocardial infarction have a chance of illness and death that is 1.5-15 times higher than that of the general population.[11] There is a substantial risk of another cardiac event in this population. Within 6 years after a recognized attack 18% of men and 35% of women will have another infarction, 7% of men and 6% of women will experience sudden death, and about 22% of men and 46% of women will be disabled with heart failure.

A complete recovery after an MI is seen in only two-thirds of patients, although 88% of those under age 65 are able to return to their usual work.[11] The U.S. health care system will spend approximately $142.5 billion in direct and indirect costs associated with coronary heart disease in the year 2006.

- Pathophysiology

Coronary artery disease (CAD) is the main process responsible for the occurrence of MI. [32,33] Fatty streaks deposit on coronary artery endothelium which progress to the formation of atherosclerotic plaques. These plaques develop, proliferate, and eventually disrupt the integrity and function of the endothelium, and may. precipitate thrombus formation. A sudden interruption of blood supply to an area of the myocardium is caused by an occlusion of a coronary artery. The occlusion eventually compromises myocardial function to the degree that it becomes necrotic. Ischemia progresses from the endocardium to the epicardium resulting in myocardium death if blood flow is not restored.

After a myocardial infarction many events take place due to the response of the left ventricle to injury. [32] These events are known as ventricular remodeling. Activation of the neurohumoral and renin-angiotensin systems and the release of vasopressin ensue once there is a decrease in cardiac output. As a response to the decrease in cardiac output sinus tachycardia occurs. It is mediated by the activation of the adrenergic

system and within hours expansion of the infarcted area occurs due to thinning and stretching of the infarcted segment. This is followed by acute dilation and hypertrophy of the noninfarcted myocardium. Chronic changes in ventricular volume which can lead to further ventricular dilation and hypertrophy can follow this process ultimately leading to the development of left ventricular failure.

- Risk Assessment and Clinical Presentation

A predominant symptom of MI is chest pain although 15% of patients following an MI may not experience chest discomfort. [32,33] Patients present with diaphoresis, nausea and vomiting, arm tingling or numbness and shortness of breath. Criteria needed to confirm the diagnosis of MI include characteristic electrocardiographic (ECG) and cardiac enzyme changes characteristic changes.

Since most myocardial infarctions result from coronary heart disease (CHD), some risk factors include hypertension, diabetes, dyslipidemia, obesity, physical inactivity, and smoking.[34]

- Approaches to Long-term Treatment

Therapies for secondary prevention are an essential part of the management of all patients following a myocardial infarction.[34,35] Smoking cessation, aggressive lipid-lowering, tight control of hypertension and diabetes, and prophylactic use of beta-blockers, ACE inhibitors, and aspirin have all demonstrated benefits in secondary prevention.

The American College of Cardiology and American Heart Association recommend for all patients with left ventricular dysfunction following a myocardial infarction to receive beta-blocker therapy beginning within a few days of the event (if not initiated acutely) and continuing indefinitely, unless they have a contraindication.[34,35] Chronic, long-term therapy with β-blockers has been shown to reduce recurrent infarction and death.[36] [37,38] [6] Patients with reduced LV function appear to benefit as much if not more than patients with normal LV function. The use of β-blockers in this patient population has also been associated with significant reductions in the likelihood of sudden death compared to similar patients not on β-blocker therapy.

- Place of *Coreg CR* in Treatment

Although the efficacy of beta-blockers in decreasing coronary events and improving outcomes in patients post-MI is well-established, and supportive data from large randomized trials exists for propranolol, metoprolol and timolol,[35,36] [37,38] no other trial studied patients post-MI with confirmed left ventricular systolic dysfunction on current standard therapies until the CAPRICORN trial. [6] Therapy with carvedilol resulted in significant reductions in all-cause and cardiovascular mortality, in addition to fatal or nonfatal reinfarction. *Coreg CR* is indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a MI and have a LVEF of ≤ 40% with or without symptomatic heart failure.

The use of once-daily *Coreg CR* may further improve patient care through improved adherence in patients post-MI with LVD who require lifetime chronic therapy with multiple medications. A multicenter analysis of 17,035 patients who had survived at least one year following a MI demonstrated that only 45% of patients were adherent to beta-blocker therapy 360 days post-discharge.[39] Minimizing the total number of daily doses has been found to be more important in promoting adherence than minimizing the total number of medications.[28] A meta-analysis of 76 studies evaluating adherence using electronic monitoring devices identified an inverse relationship between the number of daily doses and the rate of adherence.[29] Studies in this meta-analysis using drugs dosed once daily had a mean compliance rate of 79% ± 14%, whereas studies measuring adherence with twice daily dosed drugs reported mean rates of 69% ± 15%. Adherence to therapy with carvedilol has also been shown to significantly influence outcomes in patients with either post-MI LVD, heart failure, or hypertension.[40] For every 10% improvement in adherence (measured by medication possession ratio), there was an 8% reduction in cardiovascular-related and all-cause hospitalizations ($P < 0.001$).

Despite national treatment guidelines and clinical trial evidence, beta-blockers are still significantly underused in patients post-MI, particularly in patients who are at highest risk, such as those with heart failure.[41] Carvedilol is the only beta-blocker FDA-approved for use in patients post-MI with LVD, and therefore holds a unique place in therapy.

2.3 Disease Description for Hypertension

- Epidemiology

Hypertension is a significant illness affecting 32.3% (65 million) of Americans in 2003 and resulting in an estimated societal cost for 2006 of $63.5 billion.[11] Hypertension is also a known risk factor for the development of serious medical conditions such as stroke, heart failure (HF), end-stage renal disease and cardiovascular disease (CVD). Results from the Framingham Heart Study revealed hypertension have a two- to three-fold increased risk of developing HF. [42] Combining hypertension with associated clinical conditions, such as diabetes, places patients at a greater than 20% risk of developing a cardiovascular event within 10 years.[43] These risk rates are alarming, especially when considering that CVD is the leading cause of death in the U.S. and costs the healthcare system more than $403 billion in direct and indirect costs.[11]

- Pathophysiology

Many factors may contribute to the development of primary hypertension including abnormal neural mechanisms (i.e. sympathetic innervation and adrenergic stimulation), defects in peripheral autoregulation (renal defect in sodium excretion), malfunctions in either humoral or vasodepressor mechanisms (i.e. renin-angiotensin-aldosterone system), and disturbances in sodium, calcium, and natriuretic hormone. [44]

- Risk Assessment and Clinical Presentation

Patients can be identified as having hypertension if their systolic blood pressure (SBP) is 140 mmHg or greater or their diastolic blood pressure (DBP) is 90 mmHg or greater based on the average of two or more seated BP readings on each of two or more office visits.[45] Patients with uncomplicated hypertension are usually asymptomatic. As hypertension progresses, symptoms characteristic of cardiovascular, cerebrovascular, or renal disease may occur as the patient develops target organ damage.[46]

Cardiovascular risk stratification in patients with hypertension is determined by the level of blood pressure, but also the presence or absence of target organ damage (stroke, heart disease, nephropathy, peripheral artery disease and retinopathy) or other risk factors.[45] Risk factors include smoking, dyslipidemia, diabetes, age (men >55 and women >65 years), family history of premature CVD (men <55 and women <65 years), obesity (BMI >30 kg/m2), physical inactivity, and microalbuminuria or GFR <60 ml/min. Based on this assessment and the level of blood pressure, the patient's risk group can be determined. Table 3 summarizes the stages of hypertension as well as cardiovascular risk stratification in adults (age 18 and older). This classification (blood pressure stage and risk grouping) is directly linked to treatment and treatment goals.

Table 3. Staging, Risk Stratification and Treatment [47]

Risk Stratification and Treatment			
Blood Pressure Stages (mmHg)	**Lifestyle Modifications**	**Initial Drug Therapy**	
		Without Compelling Indication	**With Compelling Indication***
Normal (SBP < 120 and DBP < 80)	Encourage		
Prehypertension (SBP 120-139 or DBP 80-89)	Yes	No antihypertensive drug indicated	Drug(s) for compelling indications.†

SBP = systolic blood pressure; DBP = diastolic blood pressure; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BB = beta-blocker; CCB = calcium channel blocker

*Compelling indications include heart failure, postmyocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, and recurrent stroke prevention.

†Treat patients with chronic kidney disease or diabetes to blood pressure goal of <130/80 mmHg.

Risk Stratification and Treatment			
Stage 1 Hypertension (SBP 140-159 or DBP 90-99)	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination	Drug(s) for compelling indications.† Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed
Stage 2 Hypertension (SBP > 160 or DBP > 100	Yes	Two-drug combination for most (usually thiazide-type diuretic and ACEI or ARB or BB or CCB)	
SBP = systolic blood pressure; DBP = diastolic blood pressure; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BB = beta-blocker; CCB = calcium channel blocker *Compelling indications include heart failure, postmyocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, and recurrent stroke prevention. †Treat patients with chronic kidney disease or diabetes to blood pressure goal of <130/80 mmHg.			

- Treatment Options

A combination of lifestyle modification and pharmacologic therapy is most often used to achieve BP goals in patients with hypertension.[45] Lifestyle modifications may include weight reduction (goal BMI 18.5-24.9 kg/m2), adoption of a DASH diet (rich in fruits, vegetables, and lowfat dairy), reduction in sodium intake (<2.4 g/day), physical activity (>30 min/day), and moderation of alcohol consumption.

The treatment of hypertension often requires more than monotherapy to attain target BP goals with as many as 30% of patients needing a combination of three or more drugs.[43] Thus, there are still numerous opportunities to improve the awareness and treatment of this condition. The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) developed guidelines for the awareness, treatment and control of hypertension.[45] The goals of hypertension management are to reduce blood pressure, maintain SBP below 140 mmHg and DBP below 90 mmHg (or <130/80 mmHg for patients with diabetes or chronic kidney disease), while controlling other modifiable risk factors for cardiovascular disease.

Resistant hypertension, difficulty or failure in reaching goal blood pressure, and sudden loss of blood pressure control may be contributed to poor adherence to antihypertensive therapy.[45] A 2003 report from the World Health Organization estimated that at least 50% of patients with hypertension do not take their antihypertensive medicine as prescribed. Meta-analyses evaluating the relationship between compliance and antihypertensive therapy dosing regimens, reported significant improvements in adherence and correct dose-taking between once-daily versus twice-daily regimens.[48,49] Additionally, a review of six hypertension studies correlating adherence with treatment outcomes demonstrated that the odds of good blood pressure control among patients adherent to antihypertensive therapy compared with those who were not was 3.44 (95% CI 1.60-7.37).[50] By improving adherence, once-daily antihypertensive therapies may therefore provide better treatment effects.[40]

- Place of *Coreg CR* in Treatment

According to the JNC 7 guidelines, beta-blockers are a first line therapy option based on numerous trials demonstrating reductions in hypertension-related morbidity and mortality.[45] *Coreg CR* is indicated for the management of essential hypertension, either alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. Carvedilol has also been shown to have a neutral effect on glucose and lipids.[7,51] The American Association of Clinical Endocrinologists (AACE) Hypertension Guidelines specifically recommend the use of third generation beta-blockers or drugs that block both alpha- and beta-receptors, such as carvedilol, for the treatment of hypertension in patients with diabetes because of their vasodilatory effects and positive effects on insulin sensitivity.[52]

3. PRODUCT DESCRIPTION

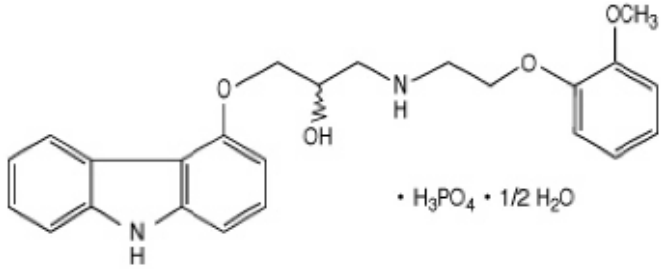
3.1 Generic Name, Brand Name and Therapeutic Class

- Product Description

Carvedilol phosphate is a nonselective ß-adrenergic blocking agent with α_1-blocking activity. It is (2RS)-1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol phosphate salt (1:1) hemihydrate. It is a racemic mixture with the following structure: (Figure 1).

Carvedilol phosphate is a white to almost-white solid with a molecular weight of 513.5 (406.5 carvedilol free base) and a molecular formula of C24H26N2O4•H3PO4•1/2 H2O.

Figure 1. Chemical Structure



Carvedilol phosphate is a white to almost-white solid with a molecular weight of 513.5 (406.5 carvedilol free base) and a molecular formula of C24H26N2O4•H3PO4•1/2 H2O.

Coreg CR is available for once-a-day administration as controlled-release oral capsules containing 10, 20, 40, or 80 mg carvedilol phosphate. *Coreg CR* hard gelatin capsules are filled with carvedilol phosphate immediate-release and controlled-release microparticles that are drug-layered and then coated with methacrylic acid copolymers. Inactive ingredients include crospovidone, hydrogenated castor oil, hydrogenated vegetable oil, magnesium stearate, methacrylic acid copolymers, microcrystalline cellulose, and povidone.

3.2 Dosage Forms , Package Sizes, NDC for all Formulations, AWP and WAC Cost per Unit

- Dosage Forms/How Supplied (National Drug Code)

Table 4. Dosage Forms of *Coreg CR*

Dosage Strength	Description	Package Size	NDC #	WAC / AWP*
10 mg	White and green capsule shell printed with GSK COREG CR and 10 mg	30	0007-3370-13	$100.09/ $125.12
		90	0007-3370-59	$300.28/ $375.35
20 mg	White and yellow capsule shell printed with GSK COREG CR and 20 mg	30	0007-3371-13	$100.09/ $125.12
		90	0007-3371-59	$300.28/ $375.35
40 mg	Yellow and green capsule shell printed with GSK COREG CR and 40 mg	30	0007-3372-13	$100.09/ $125.12
		90	0007-3372-59	$300.28/ $375.35
80 mg	White capsule shell printed with GSK COREG CR and 80 mg	30	0007-3373-13	$100.09/ $125.12
		90	0007-3373-59	$300.28/ $375.35
AWP = Average Wholesale Price; WAC = Wholesale Acquisition Price *AWP is a price calculated and reported by Facts and Comparisons, First DataBank Inc and other third party data vendors. AWP does not represent a price at which GlaxoSmithKline sells this product.				

Carvedilol phosphate should be stored at 25°C (77°F); excursions 15° to 30°C (59° to 86°F) and dispensed in a tight, light resistant container.

3.3 AHFS or Other Drug Classification

- DPS/AHFS Drug Classification

24:04 Nonselective ß-adrenergic blocking agent with selective α_1-adrenergic blocking activity.

3.4 FDA Approved Indications

- Heart Failure

Coreg CR is indicated for the treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival and, also, to reduce the risk of hospitalization.

- Left Ventricular Dysfunction Following Myocardial Infarction

Coreg CR is indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤ 40% (with or without symptomatic heart failure).

- Hypertension

Coreg CR is indicated for the treatment of essential hypertension. It can be used alone or in combination with other antihypertensive agents, especially thiazide type diuretics.

Beta-Blockers with FDA Indications For Post-Myocardial Infarction and/or Heart Failure Treatment

Table 5. Beta-Blocking Agents with FDA Indications for Post-Myocardial Infarction and/or Heart Failure Treatment[1,27,53,54,55,56,57,58) (59) (60,61) (37) (62)

Product	Post-MI	Post-MI LVD	Asymptomatic Post-MI LVD	Mild HF	Moderate HF	Severe HF
Atenolol	√* †					
Bisoprolol fumarate						
Carvedilol		√‡	√‡	√§ ll	√§ ll	√§ ll
Carvedilol phosphate		√‡	√‡	√§ ll	√§ ll	√§ ll
Metoprolol succinate				√ll ¶	√ll ¶	
Metoprolol tartrate	√* #					
Propranolol hydrochloride	√* **					

Product	Post-MI	Post-MI LVD	Asymptomatic Post-MI LVD	Mild HF	Moderate HF	Severe HF
Timolol maleate	√* ††					

MI = myocardial infarction; LVD = left ventricular dysfunction; HF = heart failure.

*Atenolol, metoprolol tartrate, propranolol hydrochloride, and timolol maleate are indicated for the reduction of cardiovascular (CV) mortality in clinically stable patients who have survived the acute phase of a myocardial infarction (MI) or are suspected to have had an MI. (Timolol is also indicated to reduce the risk of reinfarction.) The post-MI indication for these products was based on studies conducted in the late 1970s and in the early to mid-1980s. Patients with a history of heart failure (HF) or uncontrolled HF were generally excluded from these studies. Patients in these studies did not receive angiotensin-converting enzyme (ACE) inhibitors, reperfusion, thrombolytic therapy, or statins, as most of these interventions were not available or not yet proven effective at that time. Most studies did not control for concomitant medications; a small portion of patients received aspirin, diuretics, digoxin, and/or oral anticoagulants.

†Initiated intravenously (IV), then oral dose was started approximately 10 minutes after the last IV dose in patients who tolerated the full 10-mg IV dose; length of study was 7 days.(53)

‡Carvedilol and carvedilol phosphate are indicated for the reduction of CV mortality in clinically stable patients who have survived the acute phase of an MI and have a left ventricular ejection fraction (LVEF) ≤40% (with or without symptomatic HF). The indication for carvedilol in Post-MI patients with left ventricular dysfunction (LVD) is based upon a study of patients with an LVEF ≤40%; mean follow-up was 15 months. Patients in both the carvedilol and placebo groups received current standard post-MI interventions (ACE inhibitors or angiotensin II receptor blockers, diuretics, aspirin, lipid-lowering therapies, and anticoagulants).(1,55,59)

§Carvedilol and carvedilol phosphate are indicated for patients with mild to severe HF to increase survival as well as reduce the risk of hospitalization.(1,55)

‖Usually in addition to diuretics, ACE inhibitors, and digitalis.(27,55)

¶Metoprolol succinate is indicated for patients with symptomatic New York Heart Association (NYHA) Class II or III HF to decrease the rate of mortality and hospitalization; decrease is largely attributable to the reduction of the rate of CV-related mortality and hospitalization for HF.(27,60)

#Initiated IV, then oral dose was started 15 minutes after the last IV dose in patients who tolerated the full 15-mg IV dose. The efficacy of metoprolol tartrate beyond 3 months has not been conclusively established.(56)

**Initiated orally 5 to 21 days following acute MI; mean follow-up was 25 months.(37,57,61)

††Initiated orally 7 to 28 days following acute MI (either inpatient or outpatient); mean follow-up was 17 months.(62)

3.5 Use in Special Populations

Efficacy and Safety of Coreg in Patients with Hypertension and Concomitant Diabetes

The pharmacokinetic parameters of both the S(-)- and R(+)-enantiomers and predicted pharmacodynamic effects of *Coreg* and *Coreg CR* were demonstrated to be equivalent across dosage strengths and clinical status. Based on bioequivalence, *Coreg CR* is expected to offer similar efficacy and tolerability as *Coreg*.

Gemini trial

The GEMINI (*G*lycemic *E*ffects in Diabetes *M*ellitus: Carved*I*lol-Metoprolol Comparis*O*n in Hypertens*I*ves) trial was a randomized, double-blind, multicenter US trial comparing *Coreg*, a nonselective beta-blocking agent with α_1-blocking activity, to a β_1-selective blocking agent, metoprolol tartrate, to evaluate whether the differing pharmacological activity of these beta-blockers would have different effects on cardiovascular risk factors such as glycemic control, insulin resistance, and microalbuminuria in 1235 mild to moderate hypertensive patients with type 2 diabetes mellitus. (7,63) Patients receiving an angiotension-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) between the ages of 36-85 years with an HbA_{1c} of 6.5-8.5% and BP >130/80 mmHg (but <180/110 mmHg) were

randomized in a 2:3 ratio to receive *Coreg* 6.25-25 mg BID (twice daily) (n = 498) or metoprolol tartrate 50-200 mg BID (n = 737). Study medication was titrated at 1-2 week intervals toward the target blood pressure (BP) goals and then maintained for 5 months. Systolic BP targets were ≤ 135 mmHg for patients with a baseline systolic BP of 140-179 mmHg and ≤ 130 mmHg for patients with a baseline systolic BP of 130-140 mmHg. Diastolic BP targets were ≤ 85 mmHg for patients with a baseline diastolic BP of 90-109 mmHg and ≤ 80 mmHg for patients with a baseline diastolic BP of 80-90 mmHg. Hydrochlorothiazide 12.5 mg and then a dihydropyridine calcium channel blocker were added as needed to maximum doses of study medication in patients who did not reach their target BP goal.

Of the 1235 patients in GEMINI, 91% (n = 454) of patients receiving *Coreg* and 89% (n = 657) of patients receiving metoprolol tartrate were included in the modified intent-to-treat efficacy population since these patients had both baseline and on-therapy HbA_{1c} measurements for the primary endpoint analysis.[7] Maintenance therapy with 5 months of study medication was completed by 80% (n = 399) of patients receiving *Coreg* and 74% (n = 547) of patients receiving metoprolol tartrate. Baseline characteristics including age, gender, ethnicity, antidiabetic medications, and HbA_{1c} were similar between treatment groups. There was a longer treatment duration for patients receiving *Coreg*, because more patients discontinued therapy with metoprolol tartrate due to adverse events (155 ± 52 days for *Coreg* versus 147 ± 60 days for metoprolol tartrate; $P = 0.01$). Target BP was achieved with mean total daily doses of 35 mg for *Coreg* and 256 mg for metoprolol tartrate. There was no difference between treatment groups in the percent of patients who required hydrochlorothiazide 12.5 mg (43.4% for *Coreg* and 44.1% for metoprolol tartrate) or a dihydropyridine calcium channel blocker (24.7% for *Coreg* and 25.6% for metoprolol tartrate).

Glycemic Control

There was a significant 0.13% difference in the change in HbA_{1c} from baseline in favor of *Coreg* compared to metoprolol tartrate for the modified intention-to-treat analysis (Table 6). [7] Metoprolol tartrate increased HbA_{1c}, while *Coreg* did not have an effect on HbA_{1c} (Table 6). Additionally, more patients receiving metoprolol tartrate compared to *Coreg* had an elevation in HbA_{1c} of ≥ 0.5% (Odds Ratio [OR] 0.64; 95% CI 0.49-0.85, $P = 0.002$) and ≥ 1.0% (OR 0.49; 95% CI 0.30-0.70, $P < 0.001$) (Table 6). Significantly more patients withdrew from the study due to worsening glycemic control in the metoprolol tartrate group (2.2% [16/737]) compared to patients receiving *Coreg* (0.6% [3/498]; $P = 0.04$).

Table 6. Effect of *Coreg* and Metoprolol Tartrate on HbA_{1c} [7]

Treatment	n	HbA_{1c} (%)		Change from baseline (95% CI)	Difference between treatments (95% CI)	Patients with ↑ HbA_{1c} of ≥ 0.5%	Patients with ↑ HbA_{1c} of ≥ 1.0%
		Baseline	Month 5				
Coreg	454	7.21	7.21	0.02 (-0.06, 0.10) ($P = 0.65$)	-0.13 (-0.22, -0.04) ($P = 0.004$)	22%	7%
Metoprolol Tartrate	657	7.19	7.34	0.15 (0.08, 0.22) ($P < 0.001$)		30%	14.2%

Insulin Sensitivity

Insulin sensitivity (Homeostatic Model Assessment-Insulin Resistance [HOMA-IR]) improved with *Coreg* but not with metoprolol tartrate (6.0 to 5.8 µU/ml*mmol/L for *Coreg* and 5.8 to 6.2 µU/ml*mmol/L for metoprolol tartrate; treatment difference of -7.2%, 95% CI -13.8 to -0.20, $P = 0.04$). Changes in the HOMA-IR significantly correlated with changes in HbA_{1c} (r = 0.16 for *Coreg*, $P = 0.002$, versus r = 0.29 for metoprolol tartrate, $P < 0.001$). [7]

In order to determine if the beneficial effect of *Coreg* on insulin resistance (using the HOMA-IR model) was independent of insulin sensitizer (thiazolidinedione [TZD] and/or metformin) use, a separate data analysis excluding patients on insulin therapy was performed.[64] In patients on insulin sensitizer therapy, there was no effect of either treatment on insulin resistance (*Coreg*: -5.4%, 95% CI -11.9 to 1.6, $P = 0.13$; metoprolol tartrate: -2.8%, 95% CI -8.5 to 3.2, $P = 0.35$), nor a difference between treatments groups (2.6%, 95% CI

-10.7 to 6.2, $P = 0.55$). However, a significant treatment difference on insulin resistance favoring *Coreg* was evident in patients not taking a TZD and/or metformin (-15.9%, 95% CI -26.6 to -3.6, $P = 0.01$).

Microalbuminuria

The albumin:creatinine ratio (ACR), a measure of microalbuminuria (MAU), was measured in all study patients at screening and following 5 months of maintenance therapy.[7,65] In the entire cohort, there was a 16% reduction in ACR with *Coreg* compared to metoprolol tartrate (95% Confidence Interval 6% to 25%; $P = 0.003$) at the end of the study. At screening, 20% (77/388) of patients randomized to *Coreg* and 18% (98/542) of patients randomized to metoprolol tartrate had MAU, which was defined as an ACR between 30-300 mg/g. Among these patients with MAU at baseline, the reduction in ACR was similar in both groups (*Coreg*: -42.6%, 95% CI -57.3% to -22.9%, $P = 0.0003$; and metoprolol tartrate: -29.5%, 95% CI -45.2% to -9.3%, $P = 0.007$). Among the patients (79% of the study population) who did not have MAU at baseline, there was a 47% risk reduction in the development of MAU for patients receiving *Coreg* versus metoprolol tartrate (6.6% [20/302] versus 11.1% [48/431], respectively; Odds Ratio [OR] 0.53, 95% CI 0.30 to 0.93, $P = 0.03$). There was no relation between the observed changes in ACR and systolic blood pressure reduction for either *Coreg* or metoprolol tartrate (correlation coefficient = 0.2 for both).

Blood Pressure and Heart Rate

The reduction in blood pressure (BP) was similar between groups (149.4/87 mmHg to 131.3/77.1 mmHg for *Coreg* and 149.2/86.3 mmHg to 132.3/76.8 mmHg for metoprolol tartrate; P = NS). A total of 68% (310/454) of patients receiving *Coreg* and 67% (427/636) of patients receiving metoprolol tartrate reached a target BP < 130/80 mmHg.[7]

There was a 1.6% treatment difference between the effect of *Coreg* and metoprolol tartrate on heart rate (73.7 to 67.6 beats per minute [bpm] with a -6.7% change for *Coreg* and 74.5 to 66 bpm with a -8.3% change for metoprolol tartrate; treatment difference of 1.6%, 95% CI 0.70 to 2.58%, $P < 0.001$).

Lipid Levels

After 5 months, therapy with *Coreg* resulted in mean reductions in total cholesterol, LDL cholesterol, and HDL cholesterol.[7] Although there were no treatment differences between *Coreg* and metoprolol tartrate for LDL and HDL cholesterol, the differences in mean change from baseline between the treatment groups were statistically significant in favor of *Coreg* for total cholesterol (-2.88%, $P = 0.0012$) and triglycerides (13%, $P < 0.001$).[7,66]

Quality of Life

The Diabetes Symptom Checklist, a self-report questionnaire, was distributed at baseline and five months to assess diabetes-related symptoms affecting quality of life measures.[67] Thirty-five items grouped in eight dimensions (psychology [fatigue], psychology [cognitive], neuropathy [pain], neuropathy [sensory], cardiology, ophthalmology, hyperglycemia, and hypoglycemia) were scored on a dichotomous (yes/no) scale and weighted based on levels of discomfort. A significant treatment difference in the mean change from baseline in favor of *Coreg* was noted in the overall score (-0.08, 95% CI -0.15 to -0.01, $P = 0.02$), hypoglycemia (-0.12, 95% CI -0.23 to -0.02, $P = 0.02$) and hyperglycemia (-0.16, 95% CI -0.27 to -0.05, $P = 0.005$) categories.

Safety and Adverse Events

No differences were observed between treatment groups in overall safety, however, bradycardia was reported more frequently with patients taking metoprolol tartrate than *Coreg* ($P = 0.007$).[7] Significant weight gain was observed in patients receiving metoprolol tartrate compared to *Coreg* (1.2 ± 0.2 kg, $P < 0.001$, versus 0.2 ± 0.2 kg, $P = 0.36$). Reports of hypoglycemia were generated from structured surveillance of patient diaries and were similar between patient groups. Asymptomatic and symptomatic hypoglycemia were reported in 11.6% and 8.4% of patients receiving *Coreg* and 10.3% and 8.8% of patients receiving metoprolol tartrate, respectfully. Three patients receiving metoprolol tartrate also withdrew from the study due to hypoglycemia. Hyperglycemia was reported by 5.4% of patients in the *Coreg* group and 4.3% of patients in the metoprolol tartrate group.

Coreg versus Metoprolol

Ehmer et al conducted a randomized, comparative trial of *Coreg* 25 to 50 mg BID (n = 25) versus metoprolol 50 to 100 mg BID (n = 24) for 8 weeks in patients with hypertension and type 2 diabetes mellitus. [68] After 8 weeks of therapy, 92% of patients treated with *Coreg* and 83% of the metoprolol treated patients responded to therapy (diastolic blood pressure [BP] < 90 mmHg). No clinically significant changes were noted in fasting or postprandial glucose concentrations in the 49 patients who completed the study. HbA_{1C} decreased slightly during the treatment period (from 7.0% to 6.8% in the group receiving *Coreg* and from 7.6% to 7.4% in the metoprolol group). There were no reports of hypoglycemia. In addition, oral hypoglycemic agents and body weight remained constant in both treatment groups. [68]

Coreg versus atenolol

Giugliano et al conducted a randomized, double-blind trial comparing the metabolic and cardiovascular effects of *Coreg* with those of atenolol in 45 patients with hypertension and non-insulin dependent diabetes mellitus (NIDDM). [69] After a placebo run-in period, patients were randomized to receive *Coreg* 25 to 50 mg or atenolol 50 to 100 mg once daily, based on need for blood pressure (BP) reduction. Patients were evaluated at the end of the placebo run-in period and after 24 weeks of active treatment. All patients were instructed to follow a weight-maintaining diet of 50% carbohydrates, 30% lipids, and 20% protein for 3 days before each evaluation period. Forty-two patients completed the study; however, all patients were included in the study analysis on an intent-to-treat basis. Body mass index did not change in either group after treatment. BP and left ventricular mass decreased in both groups, without significant differences between the two groups ($P = 0.2$). Mean fasting plasma glucose, insulin, and HbA_{1C} concentrations decreased significantly during treatment with *Coreg* and increased during atenolol therapy ($P < 0.001$ for all values, *Coreg* versus atenolol). Total glucose disposal and insulin sensitivity index (ISI) increased during *Coreg* therapy and decreased during atenolol therapy ($P \leq 0.01$ for both values, *Coreg* versus atenolol). Serum concentrations of thiobarbituric acid reactive substance (TBARS) (a measure of oxidative stress) decreased significantly in patients receiving *Coreg* ($P < 0.001$), but did not change in the atenolol group. Neither drug prolonged hypoglycemia or glucose recovery. Glucagon and epinephrine responses to hypoglycemia were similar regardless of treatment.

Table 7. Metabolic Effects of *Coreg* Versus Atenolol in Patients with Hypertension and NIDDM [69]

	***Coreg* (n = 23)**			**Atenolol (n = 22)**		
Parameter	**Baseline**	**Change**	***P*-value**	**Baseline**	**Change**	***P*-value**
Glucose level (mmol/L)	9.1 ± 1.3	-0.3 ± 0.5*	0.01	8.9 ± 1.2	0.2 ± 0.3	<0.005
HbA_{1C} level (%)	7.6 ± 0.8	–0.1 ± 0.1*	<0.001	7.5 ± 0.9	0.3 ± 0.25	<0.001
Insulin level (pmol/L)	77 ± 46	–8.0 ± 8.0*	<0.001	69 ± 37	7.0 ± 9.0	<0.005
Insulin level during clamp (pmol/L)	538 ± 145	–44 ± 59*	0.005	503 ± 135	62 ± 49	<0.001
Insulin Sensitivity Index	0.048 ± 0.02	0.013 ± 0.007*	<0.001	0.055 ± 0.02	-0.013 ± 0.006	<0.001

Data are means ±Standard deviation

*Effect attributable to *Coreg* versus atenolol, $P < 0.001$; † Insulin sensitivity index calculated as (mmol/kg per minute)/pmol/L.

Efficacy and Safety of Coreg in African American or Black Patients with Heart Failure

US Carvedilol Heart Failure Trials Program

Yancy et al conducted a retrospective analysis of the US Carvedilol Heart Failure Trials Program to evaluate whether race influenced the response to *Coreg* in patients with heart failure (HF). [9] In this program, patients with New York Heart Association (NYHA) Class II-IV HF and left ventricular ejection fraction (LVEF) < 35% were randomized to *Coreg* (6.25 to 50 mg twice daily [BID]) or placebo for up to 15 months.

When compared with the non-black patients, black patients in this trial were younger ($P < 0.001$) and were more likely to have prior or current hypertension ($P < 0.001$), but less likely to have ischemic heart disease ($P < 0.001$). [9] In the non-black patient subgroup (n = 877), 569 patients were randomized to receive *Coreg* and 308 patients received placebo. In the black patient subgroup (n = 217), 127 patients were randomized to receive *Coreg* and 90 patients received placebo. Baseline characteristics in the *Coreg* and placebo groups were similar for non-black and black patients. After randomization, black and non-black patients achieved similar maintenance doses of *Coreg* (23 ± 13 mg BID and 21 ± 13 mg BID, respectively, $P = 0.38$) and similar durations of treatment (179 ± 91 days in blacks and 189 ± 101 days in non-blacks, $P = 0.85$).

Coreg reduced the risk of death or hospitalization for any reason by 48% in black patients and by 30% in non-black patients. [9] The risk of HF progression leading to death, hospitalization or change in medication was decreased by 54% in black and by 51% in non-black patients (Table 8). LVEF, NYHA class, and patient and physician global assessments were also improved in both black and non-black patients. For each of these endpoints, significant improvements were observed in the patients receiving *Coreg* when compared with those receiving placebo for both races ($P < 0.05$ for all analyses), and there was no significant effect of race on treatment effect ($P > 0.05$ for all race-treatment interaction analyses).

Table 8. Comparison of Major Clinical Events According to Treatment Group in Black and Non-Black Patients [9]

	Coreg **(n = 696) n (%)**	**Placebo (n = 398) n (%)**	**Relative Risk* (95% CI)**	**Within Group *P*-Value†**	**Interaction *P*- Value‡**
All-Cause Mortality					
Blacks	6/127 (4.7)	8/90 (8.9)	0.44 (0.15-1.28)	0.13	—
Non-blacks	16/569 (2.8)	23/308 (7.5)	0.32 (0.17-0.62)	<0.001	0.63
All-Cause Mortality and Hospitalization for Any Reason					
Blacks	26/127 (20.5)	33/90 (36.7)	0.52 (0.31-0.88)	0.01	—
Non-blacks	119/569 (20.9)	90/308 (29.2)	0.7 (0.53-0.92)	0.01	0.33
All-Cause Mortality and Hospitalization for Cardiovascular Reason					
Blacks	22/127 (17.3)	22/90 (24.4)	0.68 (0.37-1.23)	0.2	—
Non-blacks	95/569 (16.7)	76/308 (24.7)	0.65 (0.48-0.88)	0.005	0.89
All-Cause Mortality and Hospitalization for Heart Failure					
Blacks	12/127 (9.4)	14/90 (15.6)	0.57 (0.26-1.25)	0.16	—
Non-blacks	46/569 (8.1)	46/308 (14.9)	0.51 (0.33-0.77)	0.001	0.78
Clinical Progression of Heart Failure §					
Blacks	17/127 (13.4)	23/90 (25.6)	0.46 (0.23-0.94)	0.03	—
Non-blacks	100/569 (17.6)	92/308 (29.9)	0.49 (0.35-0.69)	<0.001	0.88

CI = confidence interval; n = number of patients

*The relative risk is the risk in the *Coreg* group relative to that in the placebo group; †*P*-values are for the comparison between the values in the placebo and *Coreg* groups within each racial cohort; ‡*P*-values for interactions are for the comparison between the effect of *Coreg* in black patients and the effects in the non-black patients; §Heart failure leading to death, hospitalization, or a sustained increase in medication.

The frequency of adverse events with *Coreg* (when corrected for placebo) was also similar in black and non-black patients, except that *Coreg* produced hypotension (without dizziness) less frequently in black patients than in non-blacks, possibly due to lower pre-treatment blood pressures in non-black patients. [9] The number of patients who discontinued treatment because of an adverse event was lower with *Coreg* than with placebo, regardless of race (7% versus 14% in *Coreg* and placebo groups, respectively, $P = 0.06$ in blacks, and 8% versus 12% in *Coreg* and placebo groups, respectively, $P = 0.02$ in non-blacks).

COPERNICUS Trial

The *C*arvedil*O*l *P*rosp*E*ctive *R*a*N*dom*I*zed *C*um*U*lative *S*urvival Study (COPERNICUS) was a multicenter, double-blind, placebo-controlled study that compared the effects of *Coreg* with placebo on all-cause mortality in 2,289 patients with advanced or severe HF. Patients were randomized to receive either *Coreg* (3.125 - 25 mg BID, n = 1156) or placebo (n = 1133). The mean duration of follow-up was 10.4 months. Baseline demographic characteristics were similar between the placebo and *Coreg* groups. [3] In the

non-black patient group (n = 2168), 1098 received *Coreg* and 1070 received placebo. In the black patient group (n = 121), 58 received *Coreg* and 63 received placebo. All-cause mortality plus hospitalization for any reason as well as other combined endpoints were comparably reduced for non-black and black patients (Table 9) as determined by Kaplan-Meier event rates.[70]

Table 9. COPERNICUS: Mortality and Combined Mortality or Hospitalization at 1-year with *Coreg* and Placebo [70]

Race	Coreg (n = 1156) n*	Placebo (n = 1133) n*	Hazard Ratio (95% CI)	*P*-Value
All-Cause Mortality				
Non-blacks	126/1098	183/1070	0.65 (0.52-0.81)	0.0002
Blacks	4/58	7/63	0.6 (0.18-2.05)	0.4147
All-Cause Mortality or Any Hospitalization				
Non-blacks	256/1098	363/1070	0.78 (0.68-0.89)	—
Blacks	15/58	29/63	0.56 (0.33-0.95)	0.0155
All-Cause Mortality or CV Hospitalization				
Non-blacks	298/1098	363/1070	0.75 (0.65-0.88)	0.0042
Blacks	16/58	32/63	0.41 (0.22-0.76)	0.0003
All-Cause Mortality or HF Hospitalization				
Non-blacks	256/1098	328/1070	0.71 (0.60-0.84)	—
Blacks	15/58	29/63	0.46 (0.25-0.86)	0.0155

CI = Confidence Interval; CV = cardiovascular; HF = heart failure; n = number of patients

*Represents number of patients experiencing the respective outcome over the total number of patients either black or non-black on the respective therapy.

COHERE

The *CO*reg *HE*art Failure *RE*gistry (COHERE) was created to collect data on outcomes and other clinical variables in a typical HF population and to observe experience with *Coreg* by community practitioners.[71] Primary outcomes of the registry included: median and one-year survival, frequency and duration of hospitalizations, frequency of emergency room visits and office/clinic visits for worsening HF, composite endpoint of death and HF hospitalizations or emergency room visits, changes from baseline in NYHA class, global assessment, vital signs, distribution of maximally tolerated *Coreg* dose at twelve months, and trends in concomitant medication use. The COHERE registry prospectively evaluated the efficacy and tolerability of 4,280 patients with HF treated with *Coreg* in the community setting. The total COHERE population was 12% black, 80% white, and 8% other racial/ethnic groups. [72] Baseline characteristics, including heart failure status, of black patients compared to white patients in COHERE are presented in Table 10.

Table 10. COHERE: Baseline Characteristics and Heart Failure Status by Race[72]

Characteristic	Black Patients (n = 523)	White Patients (n = 3,433)	*P*-value
Men, %	55	67	< 0.001
Age, years ± SD	61 ± 14	67 ± 13	< 0.001
HF treated by a cardiologist, %	66	74	< 0.001
Duration of HF (< 6 mo/ 6-12 mo/ > 12 mo), %	29/ 9/ 62	31/ 12/ 57	NS
Diabetes (comorbid), %	37	30	0.002
HF etiology (CAD/ HTN/ Idiopathic/ Other), %	31/ 38/ 20/ 11	60/ 12/ 17/ 11	< 0.001
NYHA Class (I / II/ III / IV), %	9/ 47/ 40/ 4	11/ 53/ 33/ 3	< 0.001
LVEF, mean ± SD, %	30 ± 13	31 ± 12	0.09
HF hospitalization in the prior year, %	35	26	< 0.001
CAD = coronary artery disease; EF = ejection fraction; HF = heart failure; HTN = hypertension; MI = myocardial infarction; mo = months; NS = not significant; NYHA = New York Heart Association; SD = standard deviation			

Achieved dose following titration was similar among black and white patients with approximately 80% of patients in both groups achieving a dose of at least 6.25 mg BID, and about 40% in each group reaching 25 mg BID. [72] Therapy with *Coreg* was discontinued during titration in 7% of black and 10% of white patients ($P = 0.04$). Following one year of treatment, changes in NYHA functional class or heart failure symptoms per the patient's own assessment, did not differ between black or white patients. In addition, there was no difference in the Kaplan-Meier mortality rates between the two groups at 6, 12, or 15 months after starting *Coreg* (15 month death rates: 9.1% and 8.4% for blacks and whites, respectively). Heart failure hospitalizations in the year prior to initiation of therapy with *Coreg* were significantly higher in the black patient group (Table 10), as well as in the year following COHERE enrollment (15% of black and 11% of whites were hospitalized; $P = 0.007$). The reduction in heart failure hospitalization following initiation of *Coreg*, however, was the same in both black and white patients (-58% and -56%, respectively).

Efficacy and Safety of Coreg in Elderly Patients with Heart Failure

Tolerability of Carvedilol in elderly patients with heart failure

The tolerability of initiating carvedilol was assessed in 1030 elderly patients with systolic heart failure in a multinational, prospective, six-month, observational trial.[10] Patients were enrolled into the Carvedilol Open Label Assessment (COLA II) if they were > 70 years old and considered by their treating physician to be clinically appropriate for β-blocker therapy. Tolerability was evaluated within the following age groups: 70 to 75 years, 76 to 80 years, and >80 years; and was defined as patients having received carvedilol at a dose of ≥ 6.25 mg twice daily (BID) at the end of the six-month study period, having received a minimum of three months of therapy during this period. Baseline characteristics for the three age groups are listed in Table 11.

Table 11. Baseline characteristics for the three age groups[10]

	70 to 75 years n = 402	76 to 80 years n = 310	> 80 years n = 297
Gender (% male)	60.4	56.1	41.4
NYHA Class I/II/III/IV (%)	4/ 45/ 47/ 3	4/ 44/ 47/ 6	6/ 44/ 43/ 6
LVEF (%)	36.9	38.5	38.0
Diabetes (%)	32.3	29.2	26.3
Ischemic Heart Disease (%)	60.4	60	58.6
ACE Inhibitor (%)	77.4	76.4	71.7
ARB (%)	13.2	13.9	12.5
Spironolactone (%)	25.4	22.6	21.0
Diuretics (%)	68.2	63.5	67.3
Digoxin (%)	32.6	26.8	25.9
ARB = angiotensin II receptor blocker; ACE = angiotensin converting enzyme; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association			

Following six months of therapy with carvedilol, significant reductions were seen in systolic blood pressure, diastolic blood pressure, and heart rate within each age group.[10] When measured, left ventricular ejection fraction (LVEF) significantly increased and New York Heart Association (NYHA) functional class significantly decreased within all three age groups, with no difference in response across the age ranges for either parameter.

Overall, 80% (805/1009) of patients tolerated carvedilol, however advancing age did significantly predict tolerability rates (84.3% for patients aged 70-75 years; 76.8% for 76-80 years; and 76.8% for >80 years; $P < 0.05$ for trend)[10] Achieved dose was not significantly different according to age, as patients aged 70-75 years, 76-80 years, and > 80 years achieved mean daily doses of 33.3 mg, 30.4 mg, and 29.3 mg, respectively. Reasons for discontinuation of therapy including worsening heart failure, symptomatic hypotension, bradycardia, and wheezing were also not different by age, except for death, which increased with advancing age.

The BRING-UP 2 (Beta-blockers in patients with congestive heart failure: guided use in clinical practice) study evaluated the feasibility, safety profile, and associated outcomes of carvedilol therapy in elderly patients with symptomatic chronic heart failure.[73] Consecutive outpatients at multiple centers aged ≥ 70 years without contraindications to beta-blocker treatment were considered eligible for the study and were followed for up to one year. Carvedilol was prescribed at the physicians' discretion at a dosage of 3.125-6.25 mg BID and up-titrated every 1-2 weeks to the maximum tolerated dosage. Predefined study cohorts for comparison included: 1.) patients who were already on carvedilol treatment at study entry, 2.) patients started on carvedilol, and 3.) patients not considered for beta-blocker treatment.

Of 1518 elderly patients, 505 (33.3%) were already on carvedilol, and carvedilol was newly prescribed in 419 (27.6%) patients and prescribed later during the follow-up period in 45 patients.[73] One or more clinical contraindications were noted in 378 patients, so the percent of elderly patients not prescribed beta-blockers in the absence of contraindications was 11.3%. At one year, 58.7% of surviving patients were still on carvedilol at a mean dose of 24 ± 21 mg/daily. Discontinuations took place within the first month of therapy for 46% of patients, and were primarily due to worsening heart failure (34%), hypotension (20%), or bradycardia/atrio-ventricular block (10%). Independent predictors for beta-blocker initiation included heart rate (continuous variable), sex (female versus male), and LVEF (<30% versus ≥ 30%). During the 1 year follow-up, there were no differences in the rate of worsening heart failure (15% already treated, 18% newly treated, 18% not treated), all-cause hospitalization (26%, 26%, and 31%, respectively), and myocardial infarction (2%, 2%, and 1%, respectively) between patient cohorts; however, patients not treated with a carvedilol had a significantly higher risk for death than patients who were newly started on or already treated with carvedilol (18.0% versus 11.2% newly treated and 10.8% already treated, $P = 0.0005$).

The safety and tolerability of carvedilol in elderly patients with chronic heart failure was also evaluated in a 3-month prospective randomized, open, placebo-contolled trial.[74] A total of 40 patients (28 males and

12 females, mean age 76.8 ± 5.9 years; range 68-87 years) with New York Heart Association (NYHA) II-IV heart failure of ischemic (n = 30) or nonischemic (n = 10) origin were enrolled. All patients were receiving therapy with digoxen, furosemide, and an ACE inhibitor and were randomized to either carvedilol (n = 20) or placebo (n = 20). Prior to the 12-week treatment phase, cardiac and noncardiac medications were adjusted over a 2-week period. All patients underwent clinical, functional, cognitive, and laboratory assessments at baseline , 4 weeks, and 12 weeks.

Following 12 weeks of therapy with carvedilol, systolic blood pressure , diastolic blood pressure, and heart rate all significantly decreased and LVEF significantly increased, whereas the patients taking placebo had no significant changes in any of these cardiovascular variables.[74] There was no difference in cognitive function, functional ability, or activity scores in either group throughout the study. It was also noted that none of the patients' glycemic or lipid metabolic indexes were altered during therapy with carvedilol. One patient receiving placebo and two patients receiving carvedilol withdrew from the study- the first on carvedilol due to worsening heart failure and the second due to hypotension, bradycardia, vertigo, and asthenia. The authors concluded that in conjunction with conventional therapy, carvedilol improves cardiac function in elderly patients with heart failure without worsening their cognitive and functional abilities.

The COPERNICUS (*C*arvedil*O*l *P*rosp*E*ctive *R*a*N*dom*I*zed *C*um*U*lative *S*urvival) study was a randomized, double-blind, placebo-controlled, multicenter trial that evaluated the effects of *Coreg* on morbidity and mortality in 2289 patients with severe heart failure (symptoms of heart failure at rest or on minimal exertion and an left ventricular ejection fraction [LVEF] < 25%). [4] [3] Euvolemic patients receiving diuretics and either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (if tolerated) were randomized to receive either *Coreg* 3.125 mg (n = 1156) or placebo (n = 1133) twice daily (BID) in addition to their usual medications for heart failure. The dose was increased, as tolerated, at 2-week intervals to 6.25 mg, 12.5 mg, then to a target of 25 mg BID for a mean follow-up duration of 10.4 months. In addition to the primary endpoint of all-cause death, the combined risk of death or hospitalization for any reason, for a cardiovascular reason, and for heart failure were evaluated, in addition to patient global assessments as secondary endpoints.

The COPERNICUS trial was terminated early at the recommendation of an independent Data and Safety Monitoring Board due to the significant beneficial effect of *Coreg* on survival. [3] At study end, there were 130 deaths with *Coreg* and 190 deaths with placebo, reflecting a 35% reduction in the risk of death with *Coreg* versus placebo (adjusted $P = 0.0014$). Treatment with *Coreg* compared to placebo also resulted in a 24% risk reduction in mortality or all-cause hospitalization ($P = 0.00004$), a 27% risk reduction in mortality or cardiovascular hospitalizations ($P = 0.00002$), and a 31% risk reduction in mortality or heart failure hospitalizations ($P = 0.000004$). [4] The reduction in mortality and in the combined risk of death or all-cause hospitalization with *Coreg* was similar in direction and magnitude among predefined subgroups analyzed, including patients who were < 65 years of age and ≥ 65 years of age. [3] There were 49 deaths in patients < 65 years of age in the *Coreg* group (n = 609) and 81 deaths in patients < 65 years of age in the placebo group (n = 578) (Hazard Ratio [HR] 0.55; 95% Confidence Interval [CI] 0.38-0.78). For patients ≥ 65 years of age, there were 81 deaths in the *Coreg* group (n = 547) and 109 deaths in the placebo group (n = 555) (HR 0.75; 95% CI 0.56-0.99).[75]

COMET

The *C*arvedilol *O*r *M*etoprolol *E*uropean *T*rial (COMET) was a multicenter, double-blind, randomized, parallel group study designed to directly compare the effect of *Coreg* and metoprolol tartrate on morbidity and mortality in 3029 patients with New York Heart Association (NYHA) Class II-IV heart failure (HF). [5] Enrolled patients were on stable doses of a diuretic and an ACE inhibitor and had at least one cardiovascular hospitalization within the last two years. Patients were randomized to receive either *Coreg* 3.125 mg twice daily (BID) (n = 1511) or metoprolol tartrate 5 mg BID (n = 1518) titrated at two-week intervals to target doses of *Coreg* 25 mg BID and metoprolol tartrate 50 mg BID, respectively. The mean study duration was 58 months, and the mean daily dose achieved for the *Coreg* and metoprolol tartrate groups were 41.8 mg and 85 mg, respectively. Seventy-five percent of patients receiving *Coreg*, and 78% of patients receiving metoprolol tartrate reached target doses. Baseline characteristics were similar among groups. The mean patient age was 62 years, and 80% of patients were male.

Following a mean follow-up of 58 months, the incidence of all-cause mortality was 34% (512/1511) in the *Coreg* group and 40% (600/1518) in the metoprolol tartrate group, representing a 17% risk reduction

with *Coreg* (95% Confidence Interval [CI] 7-26%; *P* = 0.0017).[5] In a predefined subgroup analysis, the reduction in all-cause mortality was similar in direction and in magnitude across all subgroups. In patients < 65 years of age, there were 207 deaths in the *Coreg* group (n = 834) and 231 deaths in the metoprolol tartrate group (n = 803) (Hazard Ratio [HR] 0.84; 95% CI 0.70-1.01). In patients ≥ 65 years of age, there were 305 deaths in the *Coreg* group (n = 677) and 369 deaths in the metoprolol tartrate group (n = 715) (HR 0.84; 95% CI 0.72-0.98).

3.6 Pharmacology

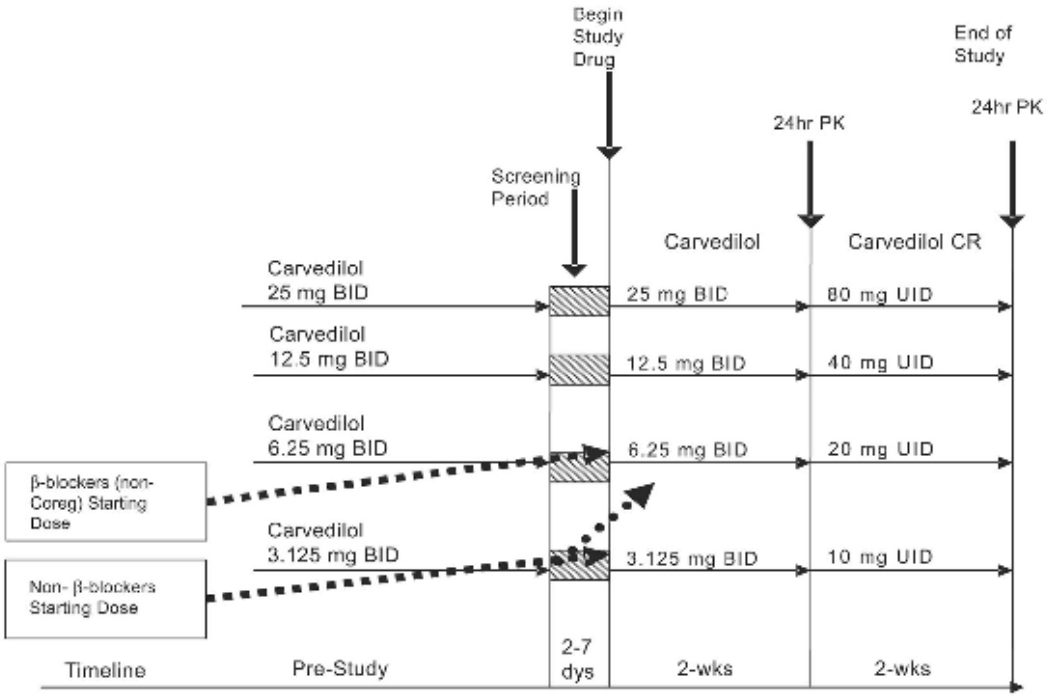
Refer to Enclosed Prescribing Information.

3.7 Pharmacokinetics/Pharmacodynamics

Pharmacokinetics and Predicted Pharmacodynamic Profile of Coreg CR In Patients with Heart Failure and Asymptomatic Left Ventricular Dysfunction

The pharmacokinetic (PK) and predicted pharmacodynamic (PD) profiles of *Coreg* and *Coreg CR* were compared in an open-label, multicenter, crossover study in 188 patients who had clinically stable heart failure (HF) (left ventricular ejection fraction [LVEF] ≤ 35%) or who had survived an acute myocardial infarction (MI) and had asymptomatic left ventricular dysfunction (LVD) (LVEF ≤ 40%).[76] Enrolled patients were screened for 2-7 days in which those already on *Coreg* received their current dose of therapy, while patients receiving no beta-blocker were started on *Coreg* 3.125 mg (HF) or 6.25 mg (post-MI LVD) twice daily (BID), and patients on another beta-blocker were switched to *Coreg*, generally starting at 6.25 mg BID. Patients also continued all appropriate background therapies. Following the screening period, subjects were stratified by clinical status (mild, moderate, or severe HF, asymptomatic post-MI LVD) and their dosage regimen for *Coreg* (3.125 mg, 6.25 mg, 12.5 mg, 25 mg BID). Patients received two weeks of therapy following which 24-hour PK assessments were completed for both the S(-)- and R(+)-enantiomers of *Coreg*. Patients were then crossed-over to an equivalent dose of *Coreg CR* for 2 weeks, and then PK assessments were repeated for both carvedilol enantiomers.

Figure 2. Study Schematic[77]



The patient population had a mean age of 61.4 ± 12.4 years, 73% were male, 35% had diabetes, and baseline mean systolic and diastolic blood pressures were 122.1 mmHg ± 18.8 and 72.8 mmHg ± 11.9, respectively.[77] A total of 174 patients completed the study and were included in the PK analyses. The

mean duration of drug exposure was 28.3 days, with the majority of patients being exposed to study medication for 11 to 17 days.[76]

The evaluated PK variables for R(+)-carvedilol and S(-)-carvedilol are summarized in Table 12 and Table 13.[76] With increasing doses of both *Coreg* and *Coreg CR*, exposure to both enantiomers increased in an approximately dose-proportional manner with minimal change in t_{max}. When data were pooled across all patients and dose groups, *Coreg* and *Coreg CR* demonstrated equivalent PK effects with point estimates equal to or close to 1.0 and 90% confidence intervals within the bioequivalence limits of 80%–125% (Table 14).

Table 12. Selected pharmacokinetic parameters for plasma R(+)-carvedilol[76]

Regimen	N	AUC (0-t)* (ng.h/mL)	C_{max}* (ng/mL)	t_{max}† (h)	C_{τ}* (ng/mL)
Coreg 3.125 mg BID	36	53.5 (79.4)	6.10 (67.1)	1.95 (0.00–6.00)	1.13 (140)
Coreg CR 10 mg QD	36	64.9 (85.8)	6.48 (92.0)	4.04 (1.00–24.00)	1.37 (114)
Coreg 6.25 mg BID	49	103 (73.4)	11.0 (61.2)	1.92 (0.00–6.03)	2.43 (107)
Coreg CR 20 mg QD	49	109 (70.0)	10.6 (58.6)	5.67 (1.00–8.00)	2.28 (106)
Coreg 12.5 mg BID	46	252 (63.6)	26.8 (58.9)	1.51 (0.00–11.75)	6.24 (97.0)
Coreg CR 40 mg QD	46	248 (70.3)	23.0 (69.0)	4.00 (0.50–12.00)	4.71 (119)
Coreg 25 mg BID	42	552 (94.0)	60.6 (70.3)	1.51 (0.50–12.00)	11.6 (144)
Coreg CR 80 mg QD	42	551 (104)	53.8 (84.6)	6.00 (3.00–16.00)	9.91 (169)

AUC (0-t) = area under the concentration-time curve; BID = twice daily; C_{τ} = trough plasma concentration; C_{max} = maximum plasma concentration; CI = confidence interval; t_{max} = time to peak concentration; QD = once daily

*Geometric mean (CVb%); †Median (range)

Table 13. Selected pharmacokinetic parameters for plasma S(-)carvedilol[76]

Regimen	N	AUC (0-t)* (ng.h/mL)	C_{max}* (ng/mL)	t_{max}† (h)	C_{τ}* (ng/mL)
Coreg 3.125 mg BID	36	20.9 (73.6)	2.27 (72.1)	1.95 (0.00–6.00)	0.52 (123)
Coreg CR 10 mg QD	36	27.7 (76.8)	2.68 (91.3)	4.04 (1.00–24.00)	0.67 (105)
Coreg 6.25 mg BID	49	43.0 (66.5)	4.33 (60.0)	1.52 (0.00–6.03)	1.24 (88.1)
Coreg CR 20 mg QD	49	48.9 (66.9)	4.35 (61.4)	5.67 (0.98–8.00)	1.24 (91.1)
Coreg 12.5 mg BID	46	108 (59.4)	11.0 (59.9)	1.50 (0.00–11.75)	3.02 (85.9)
Coreg CR 40 mg QD	46	122 (63.9)	10.2 (66.4)	4.00 (0.50–24.00)	2.82 (105)
Coreg 25 mg BID	42	242 (70.5)	25.9 (61.1)	1.50 (0.50–12.00)	6.12 (97.6)
Coreg CR 80 mg QD	42	254 (80.2)	22.7 (71.0)	6.00 (3.00–16.00)	5.72 (119)

AUC (0-t) = area under the concentration-time curve; BID = twice daily; C_{τ} = trough plasma concentration; C_{max} = maximum plasma concentration; CI = confidence interval; t_{max} = time to peak concentration; QD = once daily

*Geometric mean (CVb%); †Median (range)

Table 14. Comparisons for Select Pharmacokinetic Parameters for Pooled Data(76)

Parameter	Point Estimate for *Coreg CR*:*Coreg**	90% CI
R(+)-carvedilol		
AUC (0-t) (ng.h/mL)	1.06	1.01, 1.12
C_{max} (ng/mL)	0.95	0.89, 1.02
C_{τ} (ng/mL)	0.92	0.85, 1.01
t_{max} (h)†	3.00	2.59, 3.25
S(-)carvedilol		
AUC (0-t) (ng.h/mL)	1.16	1.10, 1.22
C_{max} (ng/mL)	1.00	0.94, 1.08
C_{τ} (ng/mL)	1.03	0.95, 1.12
t_{max} (h)†	3.00	2.73, 3.25

AUC (0-t) = area under the concentration-time curve; C_{τ} = trough plasma concentration; C_{max} = maximum plasma concentration; CI = confidence interval; t_{max} = time to peak concentration

*Point estimate for *Coreg CR*:*Coreg* is the ratio of adjusted geometric means between *Coreg CR* and *Coreg*; †Point estimate is the estimated median differences between regimens

The fluctuation index (*Coreg CR*:*Coreg* ratio for [C_{max}-C_{min}]) at steady state for both R(+)- and S(-)-carvedilol was approximately 1.0, which indicates that the peak-to-trough fluctuation in plasma concentration for once daily *Coreg CR* was similar to that of twice daily *Coreg*.(76) Additionally, the median t_{max} was approximately 3 hours longer for both enantiomers following administration of *Coreg CR* as compared to *Coreg*, which is consistent with the properties of a controlled release formulation.

The concentration-time data from this study and the PD estimates from a PK/PD model for S(-)-carvedilol developed in healthy volunteers were used to predict the beta-1 blocking effects of *Coreg* and *Coreg CR* in patients with HF.(78) Results for the predicted PD parameters are presented inTable 15 . The statistical analysis of data pooled across all patient and dose groups indicates that *Coreg CR* had an equivalent predicted PD effect compared with *Coreg*.

Table 15. Predicted Pharmacodynamic Parameters (Pooled Data)(78)

Parameter	Point Estimate for *Coreg CR*:*Coreg**	90% CI†
AUEC	1.07	1.04, 1.10
PD_{max}	0.99	0.96, 1.02
PD_{min}	1.01	0.95, 1.06

AUEC = area under the effect curve; PD_{max} = maximum pharmacodynamic effect; PD_{min} = pharmacodynamic effect at trough

*Point estimate for *Coreg CR*:*Coreg* is the difference between formulations normalized to the mean response of *Coreg*; †Lower and upper interval estimates are for the difference normalized to the mean response for *Coreg*

There were no clinically significant differences in adverse effects between the two formulations.(76) At least one adverse event was experienced by 17% of patients while receiving *Coreg* twice daily, with dizziness (2%) being the only adverse event experienced in ≥ 2% of patients.(77) Any adverse event was noted in 20% of patients receiving *Coreg CR*, with dizziness and headache being reported in 3% and 2% of patients, respectively. When switching from *Coreg* to *Coreg CR*, 11% of patients reported adverse events during the first week, with 2 reports of dizziness. Non-fatal serious adverse events occurred in 2% of patients while receiving *Coreg* and 3% of patients while receiving *Coreg CR*.

Pharmacokinetics and Pharmacodynamics of Coreg Compared to Coreg CR in the Management of Hypertension

Pharmacokinetic and pharmacodynamic comparison of *Coreg* and *Coreg CR* in patients with hypertension

In a randomized, double-blind, placebo-controlled, crossover study, Henderson et al, compared the β_1-adrenergic blocking effects of the S(-)-carvedilol enantiomer of *Coreg CR* to *Coreg* under steady state conditions by evaluating exercise-induced heart rate [HR] response during bicycle ergometry in patients

with mild to moderate essential hypertension (diastolic BP ≥ 90 mmHg and ≤ 109 mmHg and/or systolic BP ≥ 140 mmHg and ≤ 179 mmHg)[79]. Patients already receiving antihypertensive treatment were downtitrated or withdrawn from their prescribed hypertension medications ≥ 2 weeks but < 4 weeks before randomization. A total of 122 patients were randomized to receive either a constant low dose (*Coreg CR* 20 mg once daily or *Coreg* 6.25 mg twice daily) or were titrated to a high dose (*Coreg CR* 80 mg once daily or *Coreg* 25 mg twice daily) before being crossed to an equivalent dose of the alternate formulation.

Bicycle exercise testing (BET) was conducted in the supine position and individualized with respect to a workload determination test (estimated to elicit an exercise-induced heart rate [HR] of 140 beats per minute). Patients participated in a minimum of 3 BETs to become familiar with the study environment before entering the drug-free run-in phase. Baseline BET was performed 3 days prior to dosing in session 1. On day 7, in sessions 3 and 4, a total of 5 BETs were conducted before and up to 24 hours after morning medication administration and were used to evaluate the pharmacodynamic (PD) effects of both formulations and dose groups of carvedilol. Pharmacokinetic (PK) samples were also obtained after each prescribed BET. On day 8 of sessions 3 and 4, PK blood samples were obtained before dosing and periodically over the 24 hours after dosing to provide a thorough assessment of PK parameters.

The primary objective was to compare the PD and PK effects of carvedilol when administered as a extended and immediate release formulation. The PK effects of the formulations were evaluated based on area under the curve (AUC [0-t]), maximum plasma concentration (C_{max}) and trough drug concentration ($C\tau$). The PD endpoint was the percent change (PD%) from baseline in exercise-induced HR as a measure of β_1-adrenergic receptor blockade, which was estimated by evaluating PD_{min} (observed effect at trough) and PD_{max} (observed maximum effect) as well as AUEC (area under the effect curve). The safety and tolerabililty of *Coreg CR* was also evaluated after repeat dose administration. Of the 122 randomized patients, 81 provided baseline BET data and had data for PD parameter analysis, and 78 patients provided PK data for both formulations which were included in the statistical analysis of C_{max}, $C\tau$, and T_{max} for both enantiomers.

pharmacodynamic results

Mean exercise-induced HR decreased in a similar fashion between both formulations in the high- and low-dose groups and the reduction was maintained over the 24-hour dosing period. A decrease in mean exercise-induced HR was also observed across treatment periods in the placebo group, and was considered by study investigators to be due to the increase in patient familiarity with the BET technique. *Coreg* and *Coreg CR* provided equivalent results when the AUEC and PD_{max} were compared in the pooled analysis as well as across dose groups, and point estimates were at or near unity with confidence intervals between the 80-125% equivalence range demonstrating bioequivalence.

PD_{min} was measured at $C\tau$ to establish comparable effects of both formulations at the end of the dosing interval during steady state. The β_1-adrenergic blocking effects were similar between both formulations at $C\tau$. Point estimates for the ratio of *Coreg CR:Coreg* for various PD parameters are summarized in Table 16. The observed PD_{min} for both formulations were at or near unity.

Table 16. Point estimates for comparison of PD_{min}, AUEC, and PD_{max} for *Coreg* and *Coreg CR*[79]

	PD_{min}	**AUEC**	**PD_{max}**
Pooled*	1.00 (0.94-1.07)	1.02 (0.93-1.10)	0.97 (0.92-1.02)
High-dose group†	1.06 (0.97-1.15)	1.03 (0.96-1.10)	1.02 (0.95-1.08)
Low-dose group‡	0.94 (0.84-1.05)	1.00 (0.92-1.09)	0.92 (0.84-1.00)
Within-patient SD	3.86	-----	3.82

AUEC= area under the effect curve; BID= twice daily; PD_{max}= maximal pharmacodynamic effect; PD_{min}= pharmacodynamic effect at trough; QD= once daily; SD= standard deviation

*High- and low-dose groups combined

†*Coreg* 25 mg BID and *Coreg CR* 80mg QD

‡*Coreg* 6.25 mg BID and *Coreg CR* 20mg QD

Pharmacokinetic results

With increasing doses of *Coreg* and *Coreg CR* R(+) and S(-) carvedilol exposure and peak concentrations increased in a dose proportional manner. The evaluated point estimates are summarized in Table 17. In a pooled analysis for both R(+) and S(-)-carvedilol, point estimates were close to 1, and 90% CIs were within the 80%-125% equivalence range for all parameters and all analyses. Median R(+) and S(-)-carvedilol t_{max} was delayed by 3.5 hours after dosing of*Coreg CR* as compared to *Coreg*. The mean fluctuation index (*Coreg CR*:*Coreg*) of R(+)-carvedilol and S(-)-carvedilol was 1.07 and 1.04 respectively, indicating that the peak to trough fluctuation in plasma concentration for *Coreg CR* and *Coreg* was similar.

Table 17. Point estimates* for comparisons of *Coreg CR* to *Coreg* dosing for R(+)-and S(-)-carvedilol pharmacokinetic parameters(79)

Carvedilol Enantiomer	Variable	AUC (0-t)	C_{max}	Cτ	t_{max}† (hr)
R(+)-carvedilol	Pooled‡	1.06 (1.02-1.10)	0.94 (0.86-1.03)	0.89 (0.81-0.99)	3.50 (3.13-3.75)
	High-dose group§	1.05 (1.00-1.11)	0.94 (0.83-1.06)	0.85 (0.74-0.97)	3.50 (3.00-3.99)
	Low-dose group‖	1.06 (1.00-1.12)	0.94 (0.82-1.09)	0.94 (0.81-1.10)	3.44 (3.00-3.94)
	CVw%¶	14.6	35.3	38.5	----
S(-)-carvedilol	Pooled‡	1.15 (1.10-1.20)	0.95 (0.89-1.09)	0.99 (0.91-1.08)	3.50 (3.25-3.78)
	High-dose group§	1.12 (1.05-1.19)	0.97 (0.85-1.10)	0.91 (0.81-1.02)	3.50 (3.21-4.00)
	Low-dose group‖	1.18 (1.10-1.27)	1.00 (0.86-1.16)	1.08 (0.94-1.23)	3.50 (3.00-4.00)
	CVw%¶	16.7	37.4	33.7	-----

AUC(0-t)= area under the concentration-time curve from zero (pre-dose) to last time of quantifiable concentration; C_{max}= maximum plasma concentration; Cτ= trough drug concentration; t_{max}= time to maximum observed drug concentratiion

*Point estimate is the ratio of adjusted geometric means between regimens.

†Point estimate is the estimated median difference between regimens.

‡High-and low-dose groups combined.

§*Coreg* 25 mg twice daily and *Coreg CR* once daily.

¶CVw% represents a pooled estimate of within-patient variability.

‖*Coreg* 6.25 mg twice daily and *Coreg CR* 20 mg once daily.

safety

The overall incidence of treatment-related adverse events were comparable within the *Coreg* and *Coreg CR* study arms with headache being reported most frequently in both groups. (Table 18Table 23).

Table 18. Treatment-related adverse events*(79)Table 23. Treatment-related adverse events*(79)

Regimen (n%)							
	Coreg (dosed BID†)			*Coreg CR* (dosed QD†)			Placebo‡
	6.25 mg	12.5 mg	25 mg	20 mg	40 mg	80 mg	
Patients exposed	65	26	50	67	26	51	63
Patients with adverse events	18 (27.7)	5 (19.2)	14 (28.0)	17 (25.4)	1 (3.8)	7 (13.7)	16 (25.4)
Adverse Event							
Headache	11 (16.9)	3 (11.5)	10 (20)	6 (9.0)	1 (3.8)	5 (9.8)	7 (11.1)
Orthostatic hypotension	3 (4.6)	2 (7.7)	2 (4.0)	3 (4.5)	0 (0)	2 (3.9)	5 (7.9)
Dizziness	3 (4.6)	2 (7.7)	3 (6.0)	1 (1.5)	0 (0)	0 (0)	4 (6.3)
Fatigue	0 (0)	0 (0)	0 (0)	1 (1.5)	0 (0)	0 (0)	2 (3.2)
Somnolence	0 (0)	0 (0)	1 (2.0)	2 (3.0)	0 (0)	0 (0)	0 (0)
Asthenia	2 (3.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dyspepsia	1 (1.5)	0 (0)	0 (0)	1 (1.5)	0 (0)	0 (0)	0 (0)
Edema, peripheral	1 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)	0 (0)
Hypertension	1 (1.5)	0 (0)	0 (0)	1(1.5)	0 (0)	0 (0)	0 (0)
Treatment-related adverse events	26	7	20	23	1	9	22

BID = twice daily

QD = once daily

*Only the most commonly reported adverse events (considered by the investigators to be related to study medication) are listed.

†Adverse events attributed to any dose of *Coreg* or *Coreg CR* include events that were reported by patients in any treatment group who were receiving the designated regimen (session 1-4); adverse events that occurred in the downtitration period are not included (session 5).

‡Placebo group includes the downtitration period (session 5) for the 2 low-dose groups that previously received carvedilol in sessions 1-4.

Comparison of the Pharmacologic and Pharmacokinetic Properties of Beta-Blockers

Table 19. - See Appendix

3.8 Contraindications

Refer to Enclosed Prescribing Information.

3.9 Warnings/Precautions

Refer to Enclosed Prescribing Information.

3.10 Adverse Events

Refer to Enclosed Prescribing Information.

3.11 Other Clinical Considerations

Refer to Enclosed Prescribing Information.

3.12 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

3.13 Dosing and Administration

Refer to Enclosed Prescribing Information.

3.14 Co-prescribed/Concomitant Therapies

Refer to Enclosed Prescribing Information.

4. EFFICACY AND SAFETY TRIALS (FDA APPROVED INDICATIONS)

4.1 Efficacy and Safety of *Coreg CR* in Heart Failure

The heart failure (HF) indication for *Coreg CR* is based on data demonstrating the bioequivalence of *Coreg CR* and *Coreg*. In order to establish bioequivalence, the following criteria need to be met: 1.) pharmacokinetic data should be collected in the target populations; 2.) the extent of exposure or area under the curve (AUC) of *Coreg CR* relative to *Coreg* should meet standard bioequivalence requirements with point estimates between 0.8 and 1.25; 3.) the trough plasma concentration of *Coreg CR* should be at least as high as the trough concentration of *Coreg*; 4.) the trough-to-peak ratio for *Coreg CR* should not be larger than the trough-to-peak ratio seen with *Coreg*; and 5.) the inter- and intrasubject variability in AUC and maximal plasma concentration (C_{max}) should be similar for the two formulations.[85] Bioequivalence was established between *Coreg CR* and *Coreg*, as each of the above criteria were met.

Coreg has been shown to be effective in improving symptoms and reducing morbidity and mortality in patients with mild, moderate, and severe heart failure.[2] [3] [4] [5] In the US Carvedilol Heart Failure Trials (USCHFT) Program, 1,094 patients with mild to severe heart failure randomized to *Coreg* or placebo for a mean of 6.5 months demonstrated significant reductions in cardiovascular hospitalizations by 27% (95% Confidence Interval [CI] 3% to 45%, $P = 0.036$) and the combined endpoint of death or hospitalization for cardiovascular reasons by 38% (95% CI 18% to 53%, $P < 0.001$).[2] Although not a prespecified endpoint, mortality was reduced by 65% (95% CI 39% to 80%, $P < 0.001$) with 31 deaths occurring in the placebo group compared to 22 deaths in patients treated with *Coreg*.

In 2289 patients with severe heart failure randomized to *Coreg* or placebo for an average of 10.4 months, therapy with *Coreg* reduced the risk of death by 35% (95% CI 19 to 48%, $P = 0.0014$) and reduced the combined risk of death or hospitalization for any reason by 24% (95% CI 13% to 33%, $P < 0.001$), for cardiovascular reasons by 27% (95% CI 16% to 35%, $P = 0.00002$), and for heart failure by 31% (95% CI 19% to 41%, $P = 0.000004$). [4] These reductions were consistent in all subgroups examined. Additionally, significantly fewer patients in the *Coreg* group compared to the placebo group were hospitalized for any reason ($P = 0.003$), for cardiovascular reasons ($P = 0.0003$), or for heart failure ($P = 0.0001$).

Coreg has also been compared to metoprolol tartrate in a head-to-head, double blind, randomized study in 3029 patients with New York Heart Association (NYHA) Class II-IV heart failure. [5] Following a mean duration of 58 months, therapy with *Coreg* (mean achieved dose 41.8 mg) compared to metoprolol tartrate (mean achieved dose 85 mg) was associated with a relative risk reduction in all-cause mortality by 17% (95% CI 7%-26%, $P = 0.0017$), which was similar in direction and magnitude across all subgroups. Extrapolation from the survival curves suggested that *Coreg* prolonged median survival for patients by 1.4 years (95% CI 0.5 to 2.3) compared with metoprolol tartrate. No difference was demonstrated for the co-primary endpoint of all-cause mortality or all-cause hospitalization, however therapy with *Coreg* compared to metoprolol tartrate was associated with significant risk reductions in the following secondary endpoints: fatal or non-fatal myocardial infarction, cardiovascular mortality, death from stroke, sudden death, and new-onset diabetes-related adverse events.

Pharmacokinetic and predicted pharmacodynamic effects of coreg cr in patients with heart failure and post-myocardial infarction left ventricular dysfunction

The pharmacokinetic (PK) and predicted pharmacodynamic (PD) profiles of *Coreg CR* and *Coreg* were compared in an open-label, multicenter, crossover study in 188 patients who had clinically stable heart failure (HF) or had survived an acute myocardial infarction (MI) and had asymptomatic left ventricular dysfunction (LVD).[76] Enrolled patients were screened for 2-7 days in which those already on *Coreg* received their current dose of therapy, while patients receiving no beta-blocker were started on *Coreg* 3.125 mg (HF) or 6.25 mg (post-MI LVD) twice daily (BID), and patients on another beta-blocker were switched to *Coreg*, generally starting at 6.25 mg BID. Patients also continued all appropriate background therapies. Following the screening period, subjects were stratified by clinical status (mild, moderate, or severe HF, asymptomatic post-MI LVD) and their dosage regimen for *Coreg* (3.125 mg, 6.25 mg, 12.5 mg, 25 mg BID). Patients received two weeks of therapy following which 24-hour PK assessments were completed for both the S(-)- and R(+)-enantiomers of *Coreg*. Patients were then crossed-over to an equivalent dose of *Coreg CR* (10 mg, 20 mg, 40 mg, and 80 mg QD, respectively) for two weeks, and then PK assessments were repeated for both carvedilol enantiomers.

The patient population had a mean age of 61.4 ± 12.4 years, 73% were male, 35% had diabetes, and baseline mean systolic and diastolic blood pressures were 122.1 mmHg ± 18.8 and 72.8 mmHg ± 11.9, respectively.(77) A total of 174 patients completed the study and were included in the PK analyses. When data were pooled across all patients and dose groups, both the S(-)- and R(+)-enantiomers of *Coreg* and *Coreg CR* demonstrated equivalent PK effects (area under the concentration-time curve, trough plasma concentration, and maximum plasma concentration) with point estimates equal to or close to 1.0 and 90% confidence intervals all within the bioequivalence limits of 80%–125%.(76) The peak-to-trough fluctuation in plasma concentration for once daily *Coreg CR* was similar to that of twice daily *Coreg*. Additionally, the median t_{max} was approximately 3 hours longer for both enantiomers following administration of *Coreg CR* as compared to *Coreg*, which is consistent with the properties of an extended-release formulation.

The concentration-time data from this study and the PD estimates from a PK/PD model for S(-)-carvedilol developed in healthy volunteers were used to predict the beta-1 blocking effects of *Coreg* and *Coreg CR* in patients with HF.(78) The statistical analysis of data pooled across all patient and dose groups indicates that *Coreg CR* had an equivalent predicted PD effect compared with *Coreg*.

Adverse Events

There were no clinically significant differences in adverse effects between the two formulations.(76,77) Any adverse event was experienced by 17% of patients while receiving *Coreg* twice daily, with dizziness (2%) being the only adverse event experienced in ≥ 2% of patients. At least one adverse event was reported for 20% of patients receiving *Coreg CR*, with dizziness and headache being reported in 3% and 2% of patients, respectively. When switching from *Coreg* to *Coreg CR*, 11% of patients reported adverse events during the first week, with 2 reports of dizziness. Non-fatal serious adverse events occurred in 2% of patients while receiving *Coreg* and 3% of patients while receiving *Coreg CR*.

4.2 Efficacy and Safety of *Coreg CR* in Post Myocardial Infarction Left Ventricular Dysfunction

The indication for *Coreg CR* in the management of left ventricular dysfunction (LVD) following myocardial infarction (MI) is based on data demonstrating the bioequivalence of *Coreg* and *Coreg CR*. In order to establish bioequivalence, the following criteria need to be met: 1.) pharmacokinetic data should be collected in the target populations; 2.) the extent of exposure or area under the curve (AUC) of *Coreg CR* relative to *Coreg* should meet standard bioequivalence requirements with point estimates between 0.8 and 1.25; 3.) the trough plasma concentration of *Coreg CR* should be at least as high as the trough concentration of *Coreg*; 4.) the trough-to-peak ratio for *Coreg CR* should not be larger than the trough-to-peak ratio seen with *Coreg*; and 5.) the inter- and intrasubject variability in AUC and maximal plasma concentration (C_{max}) should be similar for the two formulations.(85) Bioequivalence was established between *Coreg CR* and *Coreg*, as each of the above criteria were met.

Coreg has been shown to be effective in reducing cardiovascular mortality in clinically stable patients who have survived the acute phase of a MI and have LVD. (6) The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial was a multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the long-term effects of *Coreg* on morbidity and mortality in 1959 patients who had a definite MI within the previous 21 days and a left ventricular ejection fraction (LVEF) of ≤40% (or wall motion score ≤1.3), with or without clinical evidence of heart failure (HF). At the time of randomization, patients were receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (97%); aspirin (86%); anticoagulants (20%); lipid-lowering agents (23%); diuretics (34%); and 46% underwent thrombolysis or percutaneous transluminal coronary angioplasty. (6,55) Therefore, it is important to recognize that the effects of *Coreg* observed in CAPRICORN, were in addition to these therapies. Following a mean duration of follow-up of 1.3 years, all-cause mortality was 12% in the *Coreg* group and 15% in the placebo group, representing a 23% risk reduction in patients treated with *Coreg* (95% Confidence Interval [CI] 40%, $P = 0.03$). All-cause mortality or cardiovascular hospitalization was 35% in the *Coreg* group and 37% in the placebo group, representing a 8% risk reduction in patients treated with *Coreg* (95% CI -7 - 20%, $P = 0.297$). In addition, cardiovascular mortality was 11% in the *Coreg* group and 14% in the placebo group, representing a 25% risk reduction in those patients treated with *Coreg* (95% CI 4 - 42%, $P = 0.024$). There was also a significant 40% reduction in fatal or non-fatal reinfarction in patients treated with *Coreg* (95% CI 11% to 60%, $P = 0.01$).(55) The most common patient-reported adverse events in CAPRICORN (reported in >10% of patients and more frequently with *Coreg*) included dizziness, hypotension, and worsening heart failure.(86)

Pharmacokinetic and predicted pharmacodynamic effects of coreg cr in patients with heart failure and post-myocardial infarction left ventricular dysfunction

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The patient population had a mean age of 61.4 ± 12.4 years, 73% were male, 35% had diabetes, and baseline mean systolic and diastolic blood pressures were 122.1 mmHg ± 18.8 and 72.8 mmHg ± 11.9, respectively.[77] A total of 174 patients completed the study and were included in the PK analyses. When data were pooled across all patients and dose groups, both the S(-)- and R(+)-enantiomers of *Coreg* and *Coreg CR* demonstrated equivalent PK effects (area under the concentration-time curve, trough plasma concentration, and maximum plasma concentration) with point estimates equal to or close to 1.0 and 90% confidence intervals all within the bioequivalence limits of 80%–125%.[76] The peak-to-trough fluctuation in plasma concentration for once daily *Coreg CR* was similar to that of twice daily *Coreg.* Additionally, the median t_{max} was approximately 3 hours longer for both enantiomers following administration of *Coreg CR* as compared to *Coreg*, which is consistent with the properties of an extended-release formulation.

The concentration-time data from this study and the PD estimates from a PK/PD model for S(-)-carvedilol developed in healthy volunteers were used to predict the beta-1 blocking effects of *Coreg* and *Coreg CR* in patients with HF.[78] The statistical analysis of data pooled across all patient and dose groups indicates that *Coreg CR* had an equivalent predicted PD effect compared with *Coreg*.

Adverse Events

There were no clinically significant differences in adverse effects between the two formulations.[76,77] Any adverse event was experienced by 17% of patients while receiving *Coreg* twice daily, with dizziness (2%) being the only adverse event experienced in ≥ 2% of patients. At least one adverse event was reported for 20% of patients receiving *Coreg CR*, with dizziness and headache being reported in 3% and 2% of patients, respectively. When switching from *Coreg* to *Coreg CR*, 11% of patients reported adverse events during the first week, with 2 reports of dizziness. Non-fatal serious adverse events occurred in 2% of patients while receiving *Coreg* and 3% of patients while receiving *Coreg CR*.

CASPER

Study Design

CASPER (*C*ompliance *A*nd Quality of Life *S*tudy Comparing Once-Daily Carvedilol CR and Twice-Daily Carvedilol IR in *P*atients with H*ear*t Failure) was a randomized, prospective, multicenter, three-arm, parallel group trial of 405 patients with chronic heart failure (left ventricular ejection fraction [LVEF] ≤ 40%) with mild-to-severe symptoms.[87,88,89] All enrolled subjects must have been clinically stable for at least two months on immediate-release *Coreg* 6.25 mg to 25 mg twice daily as part of their standard treatment for heart failure prior to randomization. Subjects were randomized in a 1:1:1 fashion to receive (1) their usual dose of *Coreg* dosed twice daily in a double-blind manner (Arm A), (2) the analogous dose of *Coreg CR* dosed once daily with placebo given as the second daily dose in a double-blind manner (Arm B), or (3) open-label *Coreg CR* dosed once daily for five months.

The primary objective was to evaluate and compare adherence to *Coreg* dosed twice daily and *Coreg CR* dosed once daily.[87] Secondary objectives included the evaluation and comparison of New York Heart

Association (NYHA) class, brain natriuretic peptide (BNP), quality of life, satisfaction with medication treatment, and use of hospital and emergency room services.

Results

At baseline, the mean age of patients was 65 years, 73% of patients were male, and 58% of patients also had a history of myocardial infarction.[89] The mean ejection fraction was 29%, and patients were categorized as NYHA Class I (18%), II (64%), and III (17%). Most patients were taking either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (91%), in addition to diuretics (74%), digitalis (38%), and aldosterone blockers (31%). The majority of patients were taking doses of *Coreg* towards the higher end of the dosing range, and were therefore randomized to continue the following doses of *Coreg* or equivalent doses of *Coreg CR* during the study: 6.25 mg twice daily (BID)/20 mg once daily (QD), n = 89 (22%); 12.5 mg BID/40 mg QD, n = 105 (26%); 25 mg BID/80 mg QD, n = 211 (52%).

The percentage of patients completing the trial was 92.5%, 86.8%, and 89.0% for Arms A, B, and C, respectively.[89] Following five months of therapy, no significant differences between the treatment arms were observed for changes in NYHA class, BNP levels, and measures of compliance, quality of life, or medication treatment satisfaction.[88,89]

Adverse Events

Adverse events were reported in 56% of patients who continued therapy with *Coreg* (Arm A) and 58% of patients who were switched from *Coreg* to therapy with either open-label or double-blind *Coreg CR* (Arms B and C).[88,89] Reports of specific adverse events were generally similar among the treatment groups (Table 20).[89] Additionally, there were no differences between the treatment groups in the incidence of emergency department visits, all-cause hospitalizations, and procedures during the trial.

Table 20. Adverse Events Reported in at Least 5% of Any Patient Group and Other Selected Adverse Events Deemed Clinically Relevant[89]

Adverse Event **n (%)**	***Coreg*, Double-blind** **Arm A** **n = 133**	***Coreg CR*, Double-blind** **Arm B** **n = 136**	***Coreg CR*, Open-label** **Arm C** **n = 136**
Upper respiratory tract infection*	10 (7.5%)	7 (5.1%)	1 (0.7%)
Fatigue	12 (9.0%)	7 (5.1%)	8 (5.9%)
Dizziness	8 (6.0%)	10 (7.4%)	10 (7.4%)
Diarrhea	2 (1.5%)	7 (5.1%)	2 (1.5%)
Headache	6 (4.5%)	4 (2.9%)	2 (1.5%)
Dizziness, postural	0	0	1 (0.7%)
Hypotension	3 (2.3%)	1 (0.7%)	5 (3.7%)
Syncope	2 (1.5%)	1 (0.7%)	4 (2.9%)
Dyspnea	5 (3.8%)	4 (2.9%)	6 (4.4%)
Congestive cardiac failure	4 (3.0%)	2 (1.5%)	5 (3.7%)
Bradycardia	0	1 (0.7%)	0
Any adverse event	74 (55.6%)	78 (57.4%)	79 (58.1%)
Any serious adverse event	17 (13.0%)	22 (16.3%)	17 (12.6%)
**P* = 0.014 using Fisher's Exact test to compare the three groups			

4.3 Efficacy and Safety of *Coreg CR* in the Management of Hypertension

In a randomized, double-blind, multi-center, placebo-controlled, parallel-group study, the efficacy of *Coreg CR* 20 mg, 40 mg and 80 mg once daily (QD) was compared to placebo in patients with essential hypertension.[90] Study patients met one of the following criteria: 1) essential hypertension (diastolic blood pressure [DBP] ≥ 90 mmHg and ≤ 109 mmHg) as measured by 24 hour ambulatory blood pressure monitoring (ABPM) who were not on antihypertensive treatment at screening 2) history of hypertension that was already controlled (< 90 mmHg) on antihypertensive treatment or 3) uncontrolled hypertension (DBP ≥ 90 mmHg and ≤ 109 mmHg) despite treatment with up to two antihypertensive agents, (neither

of which was β-blocker). Patients in this last category continued previous medications throughout the remainder of the study. (91)

Upon completion of a 4 week run-in/washout phase, a total of 338 patients were randomized in a 1:1:1:1 ratio to one of four treatment arms: *Coreg CR* 20 mg QD (n = 87), *Coreg CR* 40 mg QD (n = 78) (20 mg QD for 2 weeks, uptitrated to 40 mg QD for 4 weeks), *Coreg CR* 80 mg QD (n = 88) (20 mg QD for 2 weeks, uptitrated to 40 mg QD for 2 weeks and then 80 mg QD for 2 weeks), or placebo (n = 85) for 6 weeks. Following the end of six weeks of therapy, patients receiving doses >20 mg QD were downtitrated over a two week period to 20 mg QD while patients in the 20 mg *Coreg CR* arm and the placebo arm remained on their respective therapies. At the end of the 2 week downtitration phase, all medications were discontinued. ABPM was performed at baseline and at the end of treatment. Office BP was also measured with a sphygmomanometer at certain study visits. (90)

The average age of study patients was 53 years and approximately two-thirds of patients were men. The patient population consisted of 18% African Americans and 9% of patients had diabetes. The mean baseline sitting SBP was 149.5 ± 11.9 mmHg, 151.4 ± 13.6 mmHg, and 150.7 ± 12.7 mmHg for the *Coreg CR* 20 mg, 40 mg and 80 mg study arms respectively, and 149.8 ± 11.43 mmHg for placebo. The mean baseline sitting DBP was 98.3 ± 4.6 mmHg, 98.9 ± 5.4 mmHg, and 99.2 ± 5.4 mmHg for the *Coreg CR* 20 mg, 40 mg and 80 mg study arms respectively, and 99.5 ± 5.3 mmHg for placebo. (91) The primary outcome was to compare the effects of *Coreg CR* to placebo in the reduction of mean 24-hour DBP using ABPM. The primary analysis was performed using the intent-to-treat efficacy (ITTE) population (n = 337) including all patients who received at least one dose of study medication with the last observation carried forward. (90) (92)

A reduction in model-adjusted mean diastolic blood pressure (DBP) was observed at the end of uptitration for all doses of *Coreg CR* compared with a -0.4 mmHg change with placebo. An ad hoc analysis also showed a reduction in model-adjusted mean changes from baseline in systolic blood pressure (SBP) at the end of uptitration for all doses of *Coreg CR* compared to the placebo group. Table 21 shows blood pressure changes for DBP and SBP from baseline and at trough as measured by ABPM. The trend analyses for model-adjusted mean DBP and SBP reductions were statistically significant for all doses of *Coreg CR*. Trough (20-24 hours) measurements for DBP and SBP were assessed using both an office cuff and ambulatory blood pressure monitoring (ABPM). For diastolic and systolic trough values measured by ABPM, the *Coreg CR* 40 mg and 80 mg study arms were significantly different as compared to placebo. (90)

Table 21. Analysis of Change from Baseline and at Trough (20-24 hours) in Mean DBP and SBP Measured by 24 hr ABPM[90,92]

	Placebo	*Coreg CR*		
		20 mg	**40 mg**	**80 mg**
Model-adjusted change from baseline measured by 24-hour ABPM, mmHg				
DBP Mean (± SE)	-0.36 ± 0.93	-4.39 ± 0.86	-7.92 ± 0.90	-9.56 ± 0.86
Difference from Placebo, Mean*	-----	-4.03	-7.56	-9.19
95% CI*	-----	(-6.41, -1.65)	(-9.95, -5.16)	(-11.59, -6.79)
P-value	-----	0.001†	< 0.0001‡	< 0.0001§
SBP Mean (± SE)	-0.63 ± 1.42	-6.75 ± 1.31	-10.06 ± 1.37	-12.48 ± 1.32
Difference from Placebo, Mean*	-----	-6.12	-9.43	-11.84
95% CI*		(-9.75, -2.50)	(-13.07, -5.79)	(-15.50, -8.18)
P-value		0.001†	< 0.0001‡	< 0.0001§
Model-Adjusted change from baseline at trough (20-24 hours) measured by 24-hour ABPM				
DBP Mean (± SE)	0.04 ± 1.22	-2.75 ± 1.16	-5.12 ± 1.12	-7.33 ± 1.13
Difference from Placebo, Mean*	-----	-2.79	-5.15	-7.37
95% CI*	-----	(-5.95, 0.37)	(-8.31, -2.00)	(-10.53, -4.21)
P-value‖	-----	0.0834	0.0015	< 0.0001
SBP Mean (± SE)	0.09 ± 1.75	-3.22 ± 1.65	-4.77 ± 1.68	-8.35 ± 1.62
Difference from Placebo, Mean*	-----	-3.30	-4.85	-8.44
95% CI*	-----	-(7.81, 1.20)	(-9.35, -0.36)	(-12.94, -3.94)
P-value‖	-----	0.150	0.035	0.0003

ABPM = ambulatory blood pressure monitoring; CI = confidence interval; DBP = diastolic blood pressure; SBP = systolic blood pressure

* Based on ANCOVA; Change = Treatment + Center + Baseline + Disease History

† Based on Tukey trend test of *Coreg CR* 20 mg and placebo.

‡ Based on Tukey trend test of *Coreg CR* 40 mg and 20 mg and placebo.

§ Based on Tukey trend test of *Coreg CR* 80 mg , 40 mg and 20 mg and placebo

‖Based on pairwise comparisons

When trough BP (20-24 hr) was evaluated by repeated cuff measurements, significant reductions were observed for all doses of *Coreg CR* in office DBP, and in office SBP, significant reductions were seen in the *Coreg CR* 40 mg and 80 mg study arms compared to placebo. Placebo-corrected mean (± SE) reductions in sitting DBP for *Coreg CR* 20 mg, 40 mg, and 80 mg were -6.47 (± 0.87) mmHg ($P = 0.0002$), -8.08 (± 0.94) mmHg ($P < 0.0001$), and -9.54 (± 0.88) mmHg ($P < 0.0001$), respectively; (placebo, -1.73 ± 0.93 mmHg). [90] Mean (± SE) reductions observed in SBP were -5.23 (± 1.54) mmHg ($P = 0.1248$), -9.47 (± 1.66) mmHg ($P = 0.0008$), and -9.82 (± 1.55) mmHg ($P = 0.0003$) for doses of *Coreg CR* 20 mg, 40 mg, and 80 mg, respectively; (placebo, -1.86 ± 1.63 mmHg).

Changes in peak DBP and SBP were significantly different from placebo for patients receiving all three doses of *Coreg CR*. The peak effect was measured by calculating the mean of all ambulatory blood pressure values during hours 3 to 7 of the 24-hour monitoring period and was also placebo-adjusted. [91] Peak (3-7 hours) DBP (± SE) reductions were -4.21 (± 1.13) mmHg, -9.80 (± 1.15) mmHg, and -11.43 (± 1.10) mmHg for *Coreg CR* 20 mg, 40 mg and 80 mg study arms respectively, and 0.38 (± 1.18) mmHg for placebo. The corresponding values for peak (3-7 hours) SBP were -7.13 (± 1.63) mmHg, -13.69 (± 1.66) mmHg, and -15.29 (± 1.60) mmHg for *Coreg CR* 20 mg, 40mg and 80 mg respectively, and 0.00 (± 1.72) mmHg for placebo. [90]

The responder rates (percentage of patients achieving a DBP < 90 mmHg or a reduction of ≥ 10 mmHg from baseline) were 14.9% for the placebo arm and 44.7%, 53.0% and 53.3% respectively, for the patients receiving *Coreg CR* 20 mg, 40 mg, and 80 mg doses.(90) Heart rate was measured by the ABPM devices as well as during office visits. Mean baseline 24-hour ABPM-derived heart rate values (bpm) for the placebo and *Coreg CR* 20 mg, 40 mg and 80 mg groups were 81 ± 11, 80 ± 10, 80 ± 9 and 80 ± 10 respectively. During treatment, heart rate remained unchanged in the placebo group, plus 0.1 ± 6.2, but fell by 6.6 ± 5.8, 7.3 ± 6.2 and 9.9 ± 6.1 in the other groups. (91) A significant decrease in heart rate was observed using office measurements with all doses of *Coreg CR*. The difference in heart rate between baseline and week 6 was +1 beat per minute for placebo and -4.4, -4.5, and -5.7 beats per minute for *Coreg CR* 20 mg, 40 mg , and 80 mg respectively. (90)

Similar reductions in SBP and DBP were seen with all doses of *Coreg CR*, however the mean pulse pressure was still lower in patients receiving *Coreg CR* than those receiving placebo. In an ad hoc analysis, the model adjusted change in mean pulse pressure (± SE) for placebo was -0.21 (± .738), and for *Coreg CR* 20 mg, 40 mg, and 80 mg, the change was -2.36 (± .681), -2.17 (± .712), and -2.77 (± .686), respectively. (90) The difference from placebo was significant for all doses of *Coreg CR*..

The overall incidence of adverse events was similar between *Coreg CR* and placebo. The incidence of fatigue, dizziness or headache was similar between all groups (Table 22). There were two serious adverse events in patients receiving *Coreg CR*, both of which were not attributed to the use of *Coreg CR* as determined by study investigators. There were no deaths during the trial. (91)

Table 22. Adverse Events Reported by ≥2% of Subjects in the Combined *Coreg CR* Group

Adverse Event n (%)	Placebo (n = 84)	*Coreg CR* 20 mg (n = 87)	*Coreg CR* 40 mg (n = 78)	*Coreg CR* 80 mg (n = 88)	Total *Coreg CR* (n = 253)
Any adverse event	32 (38)	22 (25)	23 (29)	33 (38)	78 (31)
Nausea	0	0	1 (1)	3 (3)	4 (2)
Dizziness	1 (1)	0	1 (1)	4 (5)	5 (2)
Upper respiratory tract infection	5 (6)	1 (1)	2 (3)	2 (2)	5 (2)
Edema Peripheral	1 (1)	2 (2)	1 (1)	2 (2)	5 (2)
Fatigue	3 (4)	2 (2)	1 (1)	4 (5)	7 (3)
Cough	2 (2)	1 (1)	2 (3)	3 (3)	6 (2)
Nasopharyngitis	0	4 (5)	3 (4)	2 (2)	9 (4)
Headache	5 (6)	5 (6)	5 (6)	5 (6)	15 (6)

The safety of *Coreg CR* was also evaluated in a randomized, double-blind, placebo-controlled, crossover study, that compared the β_1-adrenergic blocking effects of the S(-)-carvedilol enantiomer of *Coreg CR* to *Coreg*. The number of patients that reported treatment-related adverse events such as headache and orthostatic hypotension did not change considerably when patients were switched from *Coreg* to *Coreg CR* (Table 18Table 23).

Table 18. Treatment-related adverse events*[79]Table 23. Treatment-related adverse events*[79]

Regimen (n%)							
	Coreg (dosed BID†)			*Coreg CR* (dosed QD†)			Placebo‡
	6.25 mg	12.5 mg	25 mg	20 mg	40 mg	80 mg	
Patients exposed	65	26	50	67	26	51	63
Patients with adverse events	18 (27.7)	5 (19.2)	14 (28.0)	17 (25.4)	1 (3.8)	7 (13.7)	16 (25.4)
Adverse Event							
Headache	11 (16.9)	3 (11.5)	10 (20)	6 (9.0)	1 (3.8)	5 (9.8)	7 (11.1)
Orthostatic hypotension	3 (4.6)	2 (7.7)	2 (4.0)	3 (4.5)	0 (0)	2 (3.9)	5 (7.9)
Dizziness	3 (4.6)	2 (7.7)	3 (6.0)	1 (1.5)	0 (0)	0 (0)	4 (6.3)
Fatigue	0 (0)	0 (0)	0 (0)	1 (1.5)	0 (0)	0 (0)	2 (3.2)
Somnolence	0 (0)	0 (0)	1 (2.0)	2 (3.0)	0 (0)	0 (0)	0 (0)
Asthenia	2 (3.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dyspepsia	1 (1.5)	0 (0)	0 (0)	1 (1.5)	0 (0)	0 (0)	0 (0)
Edema, peripheral	1 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)	0 (0)
Hypertension	1 (1.5)	0 (0)	0 (0)	1(1.5)	0 (0)	0 (0)	0 (0)
Treatment-related adverse events	26	7	20	23	1	9	22

BID = twice daily

QD = once daily

*Only the most commonly reported adverse events (considered by the investigators to be related to study medication) are listed.

†Adverse events attributed to any dose of *Coreg* or *Coreg CR* include events that were reported by patients in any treatment group who were receiving the designated regimen (session 1-4); adverse events that occurred in the downtitration period are not included (session 5).

‡Placebo group includes the downtitration period (session 5) for the 2 low-dose groups that previously received carvedilol in sessions 1-4.

5. OTHER STUDIED USES

5.1 Use of *Coreg CR* or Coreg for the Treatment of Angina

Chronic Stable Angina

Placebo-Controlled Trials

Weiss et al conducted a double-blind, multicenter, crossover trial comparing the effects of three different doses of *Coreg* to placebo on peak exercise effects in 122 patients with exertional angina. [93] After a placebo-baseline phase, patients entered into a treatment phase that included five double-blind treatment periods of two weeks each, as well as a double-blind taper period of six days. During the treatment phase, each patient received the following dosing regimens: placebo, *Coreg* 12.5 mg, *Coreg* 25 mg, and *Coreg* 50 mg, all administered twice daily. In the fifth treatment phase, period four treatment was repeated. At the end of each treatment phase, two exercise tolerance tests were performed, one at the end of the dosing interval (trough) and one two hours after the administration of the last dose of that period (peak). The primary efficacy parameters were time to angina and time to 1-mm ST-segment depression.

Patients receiving *Coreg* doses of 25 mg and 50 mg twice daily had significant delays in the time to angina onset ($P = 0.0039$ and $P < 0.0001$, respectively) compared to placebo. [93] The 12.5 mg dose of *Coreg* improved time to angina onset when compared to placebo but this difference did not reach statistical significance. In addition, all doses of *Coreg* (12.5 mg, 25 mg, and 50 mg) significantly delayed the time to 1-mm ST-segment depression ($P = 0.0061$, $P < 0.0001$, and $P < 0.0001$, respectively) when compared to placebo (Table 24). The percentage of patients who experienced an adverse event was higher among patients receiving *Coreg* (32 to 35%, depending on the dose) compared to placebo (28%). Based on these findings, the investigators concluded that *Coreg* was safe and effective in the treatment of chronic stable angina.

Table 24. Mean Exercise Treadmill Times after Placebo and *Coreg* Treatments [93])

	Baseline	Placebo	*Coreg* 12.5 mg BID	*Coreg* 25 mg BID	*Coreg* 50 mg BID
Time to angina onset (seconds)	282	316	323	337*	345†
Time to 1-mm ST depression (seconds)	283	301	322‡	313†	323†
*$P = 0.0039$; †$P < 0.0001$; ‡$P = 0.0061$ BID = twice daily					

In a randomized, double-blind, placebo-controlled trial, Jamal et al evaluated the antianginal effects of two single doses of *Coreg* (25 mg and 50 mg) in 12 patients with stable, effort-induced angina. [94] A 50 mg dose of *Coreg* increased mean exercise time and time to angina by more than two minutes ($P < 0.05$ for both values versus placebo), and a 25 mg dose of *Coreg* resulted in smaller, non-significant increases in these values versus placebo. Both doses, however, significantly increased time to 1-mm ST-segment depression ($P < 0.05$). In addition, the 50 mg dose of *Coreg* resulted in a significantly greater increase in exercise time, time to angina, and time to 1-mm ST-segment depression compared to the 25 mg dose of *Coreg* ($P < 0.05$ for all values). The investigators concluded that *Coreg* was effective in preventing or decreasing effort angina, and that this was a dose-response effect.

Three additional placebo-controlled studies evaluated the effects of *Coreg* (25 mg and 50 mg) on exercise time, time to 1-mm ST-segment depression, and time to angina in patients with chronic stable angina. [95] [96,97] In all three studies, *Coreg* resulted in significant improvements in exercise time, time to 1-mm ST-segment depression, and time to angina ($P < 0.05$ for all values) versus baseline and/or placebo values.

Comparative Trials

Slow-Release Nifedipine

In a randomized, double-blind, multicenter study, van der Does et al compared *Coreg* and nifedipine slow-release (SR) in patients with chronic stable angina. [98] Following a washout and placebo run-in period, patients were randomized to receive either *Coreg* 25 mg twice daily or nifedipine SR 20 mg twice daily for four weeks. Exercise tests were performed at baseline and after four weeks of active treatment (12 hours after the preceding dose). At study completion, 143 patients were considered evaluable.

Both agents significantly improved total exercise work, time to angina, and time to 1-mm ST-segment depression versus baseline values ($P = 0.001$ for both drugs and for all values). [98] There were no significant differences reported between the two treatment groups. However, time to angina, and time to 1-mm ST-segment depression were slightly greater in the *Coreg* group compared to the nifedipine SR group (statistical significance not reported). Fewer patients treated with *Coreg* reported adverse events compared to the nifedipine SR (8 patients versus 14 patients, respectively). In addition, the total number of adverse events reported was lower in patients treated with *Coreg* versus nifedipine SR (9 events versus 23 events, respectively).

Woodward et al also compared the effects of *Coreg* and nifedipine SR on exercise capacity in 41 patients with chronic stable angina in a randomized, double-blind, parallel group study. [99] After a placebo run-in period, patients were randomized to receive either *Coreg* 25 mg twice daily or nifedipine SR 20 mg twice daily for 28 days. Exercise capacity was measured prior to the first dose, two hours after the first dose, 12 hours after the penultimate (next to the last) dose, and two hours after the last dose (day 28).

After the first dose, both *Coreg* and nifedipine SR produced a comparable, significant increase in exercise time ($P < 0.01$ and $P < 0.05$, respectively). [99] However, after four weeks of treatment, only *Coreg* showed a significant increase in exercise time compared to placebo ($P < 0.01$). When compared with placebo, a significant increase in the time to angina was observed with both drugs during acute administration (*Coreg*, $P < 0.05$; nifedipine SR, $P < 0.01$) and chronic administration (both drugs $P < 0.01$), with no significant differences between the two drugs. The time to 1-mm ST-segment depression was significantly increased with *Coreg* compared to placebo two hours after the dose on day 1 and on day 28 (both values $P < 0.05$), but not chronically. Nifedipine SR produced a significant increase in time to 1-mm ST-segment depression

compared to placebo after chronic use (two hours after the last dose on day 28 [$P < 0.01$]), but not acutely. Adverse events reported for each drug were similar.

Verapamil

A multicenter, double-blind, parallel group study compared the antianginal effects of *Coreg* with verapamil in patients with chronic stable angina. [100] After a placebo run-in period, patients were randomized to either *Coreg* 25 mg twice daily or verapamil 120 mg three times daily for a period of 12 weeks.

After 12 weeks of therapy, both agents improved TET, time to angina, and time to 1-mm ST-segment depression from baseline. There were no significant differences between the two treatment groups in any of these parameters. [100] There was a trend, although not statistically significant, towards a slight advantage of *Coreg* over verapamil for TET (risk ratio 1.14, 90% CI: 0.85 to 1.52). Adverse events were reported in 48% of the patients receiving carvedilol (n = 126) and in 58% of the patients receiving verapamil (n = 122).

Isosorbide Dinitrate Sustained-Release

In a double-blind, randomized, 6-month multicenter study, Hauf-Zachariou et al compared the antianginal effects of *Coreg* to isosorbide dinitrate sustained-release (ISDN SR) in 187 patients with chronic stable exercise-induced angina.[101] The study had the following design: 1) a single-blind placebo period lasting for 14 days (period I); 2) a randomized double-blind active treatment period for three months, during which patients were taking either *Coreg* 25 mg twice daily or ISDN SR 40 mg twice daily; and 3) an open treatment period of an additional three months, during which patients were treated with the combination of *Coreg* 25 mg twice daily and ISDN SR 40 mg twice daily (period II). The primary efficacy variable was the TET at the end of the double-blind treatment period. In addition, time to angina and time to 1-mm ST-segment depression were also evaluated.

After three months of monotherapy (period I), both agents significantly improved TET, time to angina, and time to 1-mm ST-segment depression from baseline ($P < 0.05$ both drugs for all values).[101] However, there were no significant differences between the two treatment groups in any of these exercise test parameters. There was a trend, although not statistically significant, towards a slight advantage of *Coreg* over ISDN SR for TET and time to angina. The time to ST-segment depression was increased by a median of 60 seconds in the *Coreg* group, but remained unchanged in the ISDN SR group. When patients were switched to combination therapy (period II), additional improvements in all efficacy parameters occurred. Fewer adverse events were reported with *Coreg* (n = 93) than with ISDN SR (n = 94) (14% versus 26%, respectively).

Coreg Compared to Other Beta-blockers

Metoprolol

In a randomized, double-blind, multicenter study, van der Does et al compared the efficacy and safety of *Coreg* and metoprolol in patients with stable angina. [102] After a placebo run-in phase and baseline exercise tolerance test, patients were randomized to receive either *Coreg* 25 mg twice daily (n = 248) or metoprolol 50 mg twice daily (n = 120) for four weeks. At that time, exercise testing was repeated. If the increase in total exercise time was < 1 minute, blood pressure and heart rate were stable, and the patient was not experiencing any adverse events, the dosage was increased to either *Coreg* 50 mg twice daily or metoprolol 100 mg twice daily for an additional eight weeks. Following this treatment period, another exercise test was performed.

In both the *Coreg* and metoprolol groups, total exercise time, time to onset angina, and time to 1-mm ST-segment depression were significantly improved from baseline ($P < 0.001$ for both drugs and all values). [102] The time to 1-mm ST-segment depression was significantly longer among patients treated with *Coreg* compared to metoprolol-treated patients (–75.5 seconds for *Coreg* compared to –60 seconds for metoprolol, $P < 0.05$). Patients who received *Coreg* reported fewer adverse events compared to those patients who received metoprolol (25%, n = 248 and 30%, n = 120, respectively; $P = 0.137$).

Atenolol

Freedman et al evaluated the antianginal effects of *Coreg* and atenolol in twelve patients with stable effort-induced angina pectoris receiving single doses of *Coreg* 25 mg, *Coreg* 50 mg, atenolol 50 mg, or placebo. [103] The 50 mg dose of *Coreg* was chosen for statistical comparison with atenolol, because the

authors stated that this dose of *Coreg* approached the beta-blocking potency of atenolol. In this study, both *Coreg* 50 mg and atenolol 50 mg increased mean exercise time (24% and 34%, respectively, compared with placebo; $P < 0.05$ for both drugs versus placebo), time to angina (35% and 51%, respectively, compared to placebo; $P < 0.05$ for both drugs versus placebo), and time to 1-mm ST-segment depression (54% and 102%, respectively, compared to placebo; $P < 0.05$ for both drugs versus placebo). The difference between the two drugs was only significant for the time to 1-mm ST-segment depression ($P < 0.05$). The 25 mg dose of *Coreg* produced smaller, directionally similar changes in exercise performance that did not reach statistical significance compared to placebo, except for time to 1-mm ST-segment depression ($P < 0.05$).

In a double-blind, comparative trial, Kato et al evaluated the antianginal effects of carvedilol and atenolol in 91 Japanese patients with stable angina.[104] Eligible patients were randomized to carvedilol 20 mg once daily (n = 46) or atenolol 50 mg once daily (n = 45) for a period of 4 weeks. Efficacy parameters included evaluation of improvement in subjective symptoms, global improvement rates, electrocardiographic findings, and frequency of anginal attacks.

Following four weeks of treatment, carvedilol resulted in a trend towards improvement in subjective symptoms (reported as moderately or markedly improved in 76% of patients in the carvedilol group compared to 57% of patients in the atenolol group; $P < 0.10$); global improvement rates (defined as moderately improved or better in 74% of patients in the carvedilol group and 56% of patients in the atenolol group; $P < 0.10$), and electrocardiograhic findings during exercise (reported as improved in 31% of patients in the carvedilol group compared to 29% in the atenolol group; P = NS).[104] The frequency of anginal attacks reduced after treatment in both groups ($P < 0.001$), however the frequency of attacks was significantly lower in the carvedilol group than in the atenolol group ($P < 0.05$).

The investigators reported general safety data in terms of "no problems", "slight problems", "considerable problems", or "great problems".[104] No problems were reported in 98.1% of patients in the carvedilol group and 87.3% of patients in the atenolol group. One patient in the carvedilol group reported a slight problem with regards to safety, and six patients in the atenolol group reported a slight (n = 5) or considerable (n = 1) problem with respect to safety ($P < 0.05$). Adverse reactions were reported in two patients taking carvedilol and in five patients taking atenolol (P = NS). The authors concluded that carvedilol provided similar or greater efficacy than atenolol for the treatment of effort-induced angina.

Propranolol/Isosorbide Dinitrate

In a randomized, double-blind, parallel-group study, Nahrendorf et al compared the long-term antianginal effects of *Coreg* to the combination of propranolol and isosorbide dinitrate (ISDN) in males with chronic stable angina. [105] Following baseline exercise tests with placebo, patients were randomized to receive either *Coreg* 25 mg twice daily (n = 21) or propranolol 80 mg twice daily plus ISDN 20 mg twice daily (n = 10) for six months. Additional exercise tests were performed two hours after the first dose, and after 1, 3, and 6 months of treatment. Twenty-seven patients were considered evaluable for efficacy ().

Table 25. Effects of *Coreg* versus Propranolol/Isosorbide Dinitrate on Total Exercise Time and Time to 1-mm ST-Segment Depression [105]

	TET (seconds)	TST (seconds)
Coreg (n = 20)		
Placebo Baseline	321	240
First dose (2 hours post dose)	435*	360*
6 months (12 hours post dose)	409*	360*
Propranolol + ISDN (n = 7)		
Placebo Baseline	372	210
First dose (2 hours post dose)	569*	480*
6 months (12 hours post dose)	395	240

ISDN = isosorbide dinitrate; TET = total exercise time; TST = time to 1-mm ST-segment depression.

*$P < 0.01$ versus placebo baseline

Patients receiving either *Coreg* or the combination of propranolol/ISDN had a significant improvement in both TET and time to 1-mm ST-segment depression two hours after the first dose ($P \leq 0.01$ for both drugs). [105] These effects were more pronounced following the first dose in the propranolol/ISDN group

than in patients treated with *Coreg* when compared to placebo; however, the differences between *Coreg* and propranolol/ISDN were not statistically significant. After 6 months of treatment, exercise test results carried out 12 hours after dosing were not significantly different from the placebo baseline values in the propranolol/ISDN group. In contrast, increases in TET and the time to 1-mm ST-segment depression were maintained during chronic treatment with *Coreg* compared to placebo ($P < 0.01$ for both values). The authors attributed the results in the propranolol/ISDN combination group to the development of nitrate tolerance.

Unstable angina

Brunner et al conducted a randomized, double-blind, multicenter study evaluating the efficacy of *Coreg* in patients with unstable angina. [106] Patients received either *Coreg* (25 mg twice daily, n = 59) or placebo (n = 57) for 48 hours in addition to standard therapy (e.g. intravenous nitrates, intravenous heparin, and aspirin) and were monitored in a coronary care unit. The frequency, duration, and severity of each ischemic episode were recorded by means of a 48-hour Holter monitor. *Coreg*, as adjunctive therapy, significantly reduced mean heart rate in the first 24 hours and over the 48-hour study period ($P < 0.05$ versus placebo for both time frames). Myocardial ischemia occurred in 15% (9/59) of the patients treated with *Coreg*, and in 25% (14/57) of the patients in the placebo group ($P < 0.05$). The total mean number of ischemic events and mean duration of ischemia were significantly reduced by 66% and 76%, respectively, in patients treated with *Coreg* compared to placebo (both values, $P < 0.05$). Adverse events requiring withdrawal of therapy were observed in 14% of patients receiving *Coreg* and in 9% of patients receiving placebo (P = NS). Based on these findings, the investigators concluded that the addition of *Coreg* to standard therapy effectively reduced the ischemic burden in patients with unstable angina. However, the authors noted that the addition of *Coreg* required close monitoring of heart rate and blood pressure in patients at risk for bradycardia and hypotension.

Additional considerations

Patients taking *Coreg* or *Coreg CR* should avoid abrupt cessation of therapy.[1,55] Following abrupt cessation of therapy with certain beta-blocking agents, severe exacerbations of angina pectoris, and in some cases, myocardial infarction or ventricular arrythmias have occurred. As with other beta-blockers, the dosage of *Coreg* or *Coreg CR* should be reduced gradually over a one to two week period, and the patient should be carefully monitored. If the angina worsens or acute coronary insufficiency develops, it is recommended that *Coreg* or *Coreg CR* be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue *Coreg* or *Coreg CR* therapy abruptly even in patients treated only for hypertension or HF.

5.2 Use of *Coreg* or *Coreg CR* for the Treatment of Atrial Arrhythmias

background

Carvedilol is a nonselective, competitive, adrenergic inhibitor with affinity for $beta_1$, $beta_2$ and $alpha_1$ receptors. [107] [108] Select beta-blocking agents, such as carvedilol, metoprolol succinate, and bisoprolol, have demonstrated a significant decrease in the risk of all-cause mortality, including risk of sudden arrhythmic death, in patients with heart failure (HF). In addition to its adrenergic properties, carvedilol possesses electrophysiological and antioxidant effects that have been suggested to result in additional antiarrhythmic actions. The clinical relevance of these properties has not been determined.

The predominant electrophysiological effect of carvedilol is related to its Vaughan Williams Class II dose-related antiadrenergic effects. [107] [108] Secondary electrophysiological effects include direct membrane-stabilizing activity (Class IA), prolonging repolarization by blocking potassium channels (Class III), and inhibiting L-type calcium channels (Class IV). The combination of the above electrophysiological effects results in moderate prolongation of action potential duration and effective refractory period, slowing of atrioventricular conduction, and reducing the dispersion of refractoriness.

Atrial arrhythmias

Effect on Ventricular Rate Control

In a double-blind, randomized, placebo-controlled trial, Khand et al evaluated the effect of *Coreg*, digoxin, and their combined use on left ventricular ejection fraction (LVEF), ventricular rate control, and symptom

scores in 47 patients with atrial fibrillation (AF) (> 1 month) and heart failure (HF) currently treated with digoxin. [109] HF was characterized by at least 2 months of HF symptoms and echocardiographic evidence of cardiac dysfunction (LVEF < 40% or preserved LV systolic dysfunction with LV hypertrophy, suggesting diastolic dysfunction). Patients with a heart rate (HR) < 60 beats per minute (bpm), systolic blood pressure (BP) < 90 mm Hg, serum creatinine > 250 µmol/L, sick sinus syndrome or complete heart block, current treatment with a beta-blocker, HR-lowering calcium channel blocker, greater than 200 mg amiodarone, recent major cardiovascular event or procedure, asthma, reversible obstructive airway disease, or significant hepatic disease were excluded. In Phase I of the study, patients were randomized to receive either *Coreg* in conjunction with digoxin (Group A; n = 24), or placebo in conjunction with digoxin (Group B; n = 23) for 4 months. *Coreg* was titrated from 3.125 mg twice daily (BID) at 2-week intervals to a target dose of 25 mg BID (50 mg BID in patients > 85 kg). In Phase II of the study, baseline digoxin was replaced by placebo for 2 months (Group A) in order to evaluate the effects of *Coreg* alone. No change in digoxin was made in the placebo group (Group B).

At baseline, the mean LVEF was 24% and the mean serum digoxin concentration was 1.55 mmol/L (carvedilol treatment group). [109] In Phase I of the study, the combination of *Coreg* and digoxin (Group A) improved symptom scores ($P < 0.05$), LVEF ($P < 0.05$), and New York Heart Association (NYHA) Class ($P = 0.08$) and lowered the mean 24 hour ventricular rate ($P < 0.0001$) compared with digoxin alone (Group B) (Table 26). Three patients receiving the combination of *Coreg* and digoxin (Group A) withdrew from the study due to adverse events (bronchospasm, fatigue, and gastrointestinal disturbance) and one patient receiving digoxin alone (Group B) withdrew from the study (self-withdrawal). In Phase II of the study, there was no significant difference in these endpoints between *Coreg* alone and digoxin alone (Table 26). However, symptom scores of patients who remained on therapy favored *Coreg* ($P = 0.007$). Four patients withdrew from the study in Phase II due to worsening symptoms of HF (3 in the *Coreg* alone group and 1 in the digoxin alone group).

Table 26. Results of *Coreg*, Digoxin and Combination Therapy in the Treatment of AF and HF [109]

		24-hr mean heart rate (bpm)	LVEF (%)	Symptom score*
Baseline Values	Pre- *Coreg* group	81.8 ± 11.7	23.7 ± 10.4	12 (7.25-17)
	Placebo group	75.9 ± 12	24.7 ± 9.5	10 (4-17)
Phase 1 (at 4 months)	Combination	65.2 ± 15‡	30.6 ± 9.6 ‡	7 (3-12.5)‡
	Digoxin	74.9 ± 11.2	26 ± 12.4§	8 (3-15)
	P-Value†	< 0.0001	0.048	0.039
Phase 2 (at 6 months)	*Coreg*	88.8 ±18.7	21.6 ± 11	6 (2-17)‡
	Digoxin	75.7 ±10.6	27.2 ± 11.7	8 (5-15.5)
	P-Value†	0.13	0.15	0.08

bpm = beats per minute; Combination = combination treatment with *Coreg* and digoxin; LVEF = left ventricular ejection fraction.

Data are presented as the mean value ± SD or median value (interquartile range)

* In Phase II, patients withdrawn due to worsening heart failure were assigned New York Heart Association Class IV and maximum symptom scores of 33 each;

†*P*-value is a test of significance for the change from baseline between the respective groups;

‡ Intragroup changes compared with baseline, $P < 0.05$;

§ One patient in this group, Phase I, had a technically inadequate radionuclide ventriculogram.

Agarwal et al evaluated the use of *Coreg* to control the rapid ventricular rate occurring during exercise in 28 patients with NYHA Class II HF due to idiopathic dilated cardiomyopathy.[110] Patients had co-morbid AF for a period of ≥2 years and were already receiving digoxin therapy in addition to other HF therapies including furosemide and angiotensin converting enzyme (ACE) inhibitors. All patients were anticoagulated and had not previously received a beta-blocker. Fourteen patients received placebo and 14 patients received *Coreg* 6.25 mg BID, titrated in two steps over 4 week intervals to a maximum target dose of 12.5 mg BID. All patients had an exercise test and echocardiogram performed at baseline and after 3 months of therapy. All patients treated with *Coreg* showed improved ventricular rate control (VRC).

Significant reductions in heart rate at rest (HRr) and during maximal exercise (HRm) were observed in patients receiving *Coreg* (22% and 11%, respectively; *P* = 0.001 for both values). Total exercise time (TET) was also significantly improved by 12% (*P* = 0.001) in patients treated with *Coreg*. In addition, there was no change in HF status among patients treated with *Coreg*. HRr, HRm, and TET were not improved in the control group. Neither treatment group reported significant changes in LVEF or LV diastolic dimension. The investigators concluded that the addition of *Coreg* to digoxin was beneficial in VRC in AF during exercise in patients with dilated cardiomyopathy.

Heart Failure Patients with Atrial Arrhythmias - Effects on Morbidity and Mortality

A retrospective analysis by Joglar et al evaluated a subset of patients with AF from the U.S. Carvedilol HF Trials Program.[111] A total of 84 patients with AF were randomized to receive *Coreg* and 52 were randomized to receive placebo. The percentage of patients receiving digoxin was similar in both groups (100% with *Coreg* and 96% with placebo). Nineteen percent of the patients randomized to the *Coreg* group converted to normal sinus rhythm compared to 15% of the patients randomized to the placebo group (*P* = 0.297). Of the patients remaining in AF, the reduction in HRr tended to be greater among patients treated with *Coreg* versus patients treated with placebo (13 bpm versus 7 bpm, respectively; *P* = 0.111). In addition, treatment with *Coreg* in patients with AF resulted in a statistically significant improvement in LVEF (23% to 33%; n = 69) compared to placebo (24% to 27%; n = 39) (*P* = 0.001). Physician global assessment was also significantly improved among patients treated with *Coreg* versus patients treated with placebo (71% versus 48%; *P* = 0.025). Patients with AF treated with *Coreg* had a trend towards a reduction in the combined endpoint of death or HF hospitalization versus placebo (7% and 19%, respectively; *P* = 0.055). In addition, there was a trend for *Coreg* to reduce overall mortality from 12% in the placebo group to 4.8% in the *Coreg* group (*P* = 0.12).

COMET (Carvedilol Or Metoprolol European Trial) was a multicenter, double blind, randomized parallel group trial designed to directly compare the effects of *Coreg* and metoprolol tartrate on morbidity and mortality in 3029 patients with NYHA Class II-IV HF. [5] Patients were randomized in a 1:1 fashion to receive either *Coreg* 3.125 mg BID (n = 1511) or metoprolol tartrate 5 mg BID (n = 1518) titrated at two-week intervals to a target dose of *Coreg* 25 mg BID or metoprolol tartrate 50 mg BID. Swedberg et al evaluated patients from COMET to determine the prognostic relevance on outcomes of the presence of AF at baseline (n = 600) compared with no AF (n = 2429) and the impact of new-onset AF during follow-up.[112] The presence of AF at baseline electrocardiogram (ECG) compared with no AF was associated with significantly increased all-cause mortality over a 5-year follow-up period (Relative Risk [RR] 1.29, 95% Confidence Interval [CI] 1.12-1.48, *P* = 0.0004). All-cause mortality was reduced in patients with AF by 17% with *Coreg* compared to metoprolol tartrate (RR 0.836, 95% CI 0.74-0.94, *P* = 0.0042). Treatment with *Coreg* or metoprolol tartrate did not affect the incidence of new-onset AF (*P* = 0.2).

Coreg vs Bisoprolol for Sinus Rhythm Maintenance after Cardioversion of Persistent Atrial Fibrillation

In a randomized, double-blind trial, Katritsis et al evaluated the effects of *Coreg* versus bisoprolol in maintaining sinus rhythm after successful cardioversion of persistent AF (> 7 days). [113] Exclusion criteria included LVEF < 30%, concomitant treatment with Class I or III antiarrhythmic agents, amiodarone use within 3 months before randomization, previous treatment with bisoprolol or *Coreg*, contraindications to beta-blockade, age > 80 years, or terminal illness. Pharmacologic cardioversion with oral propafenone (in the absence of ischemic heart disease) or intravenous ibutilide was initially attempted and if failed, electrical cardioversion was used. Patients were randomized to *Coreg* 25 mg BID (or *Coreg* 12.5 mg BID, LVEF < 40%) or bisoprolol 10 mg daily (or bisoprolol 5 mg daily, LVEF < 40%). Reductions in dose were permitted based on clinical status. Following randomization and initiation of drug therapy, patients were followed on an outpatient basis at 1, 3, 6 and 12 months after recruitment or at the time of AF recurrence. A total of 82 patients completed the study, 39 patients (48%) assigned to *Coreg* and 43 (52%) assigned to bisoprolol. The intention-to-treat analysis showed 17 patients (32%) receiving *Coreg* and 23 patients (46%) receiving bisoprolol relapsed into AF during the first year of total follow-up (*P* = 0.486). The cumulative AF relapse rate during the first 30 days was 31% with *Coreg* and 35% with bisoprolol (*P* = 0.69), and during the first 180 days, the relapse rate was 42% and 52%, respectively (*P* = 0.357). In patients who underwent electrical cardioversion (n = 34; 33%), 5 of 15 patients (33%) receiving

Coreg relapsed into AF compared with 8 of 19 patients (42%) in the bisoprolol group ($P = 0.601$). No statistically significant difference between the 2 treatment arms for the prevention of AF relapse was revealed through the multivariate survival analysis. Patients treated with *Coreg* had a 14% lower risk of AF recurrence compared with patients in the bisoprolol group (HR 0.86, 95% CI 0.454-1.636, $P = 0.661$); however, the results were statistically insignificant, after controlling for patient gender, age, baseline heart rate and left atrial diameter.

The crucial cut-off point for HR was determined to be 72 bpm when study groups were combined. [113] Patients with HR values < 72 bpm had a twofold higher risk of relapse into AF compared with those with HR values > 72 bpm (HR 1.74, 95% CI 0.94-3.27) as revealed by survival analysis. This finding was less prominent with *Coreg* (HR 1.52, 95% CI 0.58-3.99) compared to bisoprolol (HR 1.92, 95% CI 0.79-4.68). In addition, the mean HR was 64.2 + 10.3 bpm with *Coreg* compared to 57.8 + 7.1 bpm with bisoprolol for patients who remained in sinus rhythm ($P = 0.026$). Lower baseline changes in HR values were evident with *Coreg* compared to bisoprolol (–8.6 + 11.4 versus -13.8+ 4.5 bpm, respectively; $P = 0.064$). Due to adverse events such as symptomatic bradycardia (<45 bpm), sexual dysfunction, and undue tiredness, five patients (n = 2 for *Coreg* and n = 3 for bisoprolol) were withdrawn from the study. Eight patients (n = 3 for *Coreg* and n = 5 for bisoprolol) required a dose reduction to half of the initially prescribed regimen. Treatment was well tolerated in the remainder of the patients. Based on these findings, the investigators concluded that patients receiving *Coreg* had a 14% lower risk of AF compared with bisoprolol, although these results were not significant after adjusting for age, gender, HR, and left atrial diameter.

Atrial Arrhythmias in Post-MI Patients with LVD

The CAPRICORN (*CA*rvedilol *P*ost-Infa*R*ct Surv*I*val *CO*nt*R*ol in LV Dysfunctio*N*) trial was a multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the long-term efficacy of *Coreg* in 1959 post-myocardial infarction (MI) patients with left ventricular dysfunction (LVD), with or without clinical evidence of heart failure (HF). [6] Patients with a definite MI within the previous 21 days and a left ventricular ejection fraction (LVEF) of ≤40% (or wall motion score ≤ 1.3) treated with an ACE inhibitor were randomized to receive either *Coreg* (n = 975) or placebo (n = 984). *Coreg* was initiated at 6.25 mg twice daily (BID), but could be reduced to 3.125 mg BID if not tolerated. *Coreg* was up-titrated at 3 to 10 day intervals to the maximum dose tolerated or 25 mg BID. Patients were evaluated as outpatients at 3 month intervals during the first year and at 4 month intervals thereafter. The mean duration of follow-up was 1.3 years.

The study reported that all-cause mortality was 12% with *Coreg* and 15% with placebo, representing a 23% risk reduction in patients treated with *Coreg* (95% CI 2 - 40%, $P = 0.03$). [6] In addition, the co-primary endpoint of all-cause mortality or cardiovascular hospitalization was 35% with *Coreg* and 37% with placebo, representing a 8% risk reduction in patients treated with *Coreg* versus placebo (95% CI -7 - 20%, $P = 0.296$). A retrospective, post-hoc blinded analysis of patient-reported adverse events and serious adverse events in this trial was conducted in order to evaluate the effect of *Coreg* on cardiac arrhythmias.[114] Electrocardiogram confirmation was not available. All events considered to be related to an atrial arrhythmia were assigned to one of the following categories: a) all supraventricular ectopic beats, atrial tachycardia, atrial flutter, atrial fibrillation (AF), or any supraventricular arrhythmias (SVA), excluding sinus tachycardia and b) AF/flutter alone. Analyses were based on time-to-first event.

At the time of randomization, a total of 96 (5%) patients were receiving an antiarrhythmic agent (primarily amiodarone). The comparable rates of SVA, AF, and atrial flutter in both treatment groups are noted in Table 27.

Table 27. Effects of *Coreg* on Atrial Arrhythmias in Post-MI Patients with LVD[114]

Arrhythmia	*Coreg* n = 975	Placebo n = 984	HR (95% CI)	Log-Rank *P*-Value
All SVA	26	54	0.48 (0.30-0.76)	0.0015
AF/AFl	22	53	0.41 (0.25-0.68)	0.0003

AF = atrial fibrillation; AFl = atrial flutter; CI = confidence interval; HR = hazard ratio; n = number of patients; SVA = supraventricular arrhythmias.

A significant reduction in the combined outcomes of death or SVA and death or AF/atrial flutter was reported in patients treated with *Coreg* compared to placebo.[114] The combined outcome of death or SVA was reported in 133 patients treated with *Coreg* compared to 187 patients in the placebo group (hazard ratio [HR] 0.70, 95% CI 0.56-0.88; *P* = 0.0016). Excluding patients with a history of AF or atrial flutter, death or SVA was reported in 112 and 152 patients receiving *Coreg* and placebo, respectively (HR 0.72, 95% CI 0.57-0.92; *P* = 0.0090). Death or AF/atrial flutter was reported in 129 patients treated with *Coreg* and 186 patients in the placebo group (HR 0.68, 95% CI 0.55-0.85; *P* = 0.0008). Excluding patients with a history of AF or atrial flutter, death or AF/atrial flutter was reported in 109 and 151 patients treated with *Coreg* and placebo, respectively (HR 0.71, 95% CI 0.55-0.91; *P* = 0.0057).

5.3 Use of *Coreg* or *Coreg CR* in the Treatment of Ventricular Arrhythmias

Ventricular Arrhythmias

Patients with Heart Failure, Hypertension, Coronary Artery Disease, and Stable Angina

Cice et al conducted a six-month, randomized, double-blind, placebo-controlled study to evaluate the effects of *Coreg* in patients with ischemic or idiopathic dilated cardiomyopathy and complex VAs (Lown class III-V). [115] All patients had symptomatic HF with a left ventricular ejection fraction (LVEF) < 35% and were receiving either digoxin, diuretics, angiotensin converting enzyme (ACE) inhibitors, and/or nitrates. Prior to randomization, patients entered a two-week run-in phase in which *Coreg* 6.25 mg BID was administered to determine patient tolerance to therapy. Patients who tolerated therapy were randomized to receive either *Coreg* (titrated to a final dose of 25 mg BID or 50 mg BID for patients > 85 kg) or placebo. All patients underwent 48-hour Holter monitoring and Doppler echocardiography (ECG) at baseline and after one, three, and six months of therapy with *Coreg*. At the end of six months, 135 patients had completed the study and were evaluated for efficacy and safety (Table 28).

At one month, in patients with both ischemic and idiopathic dilated cardiomyopathy, treatment with *Coreg* significantly reduced the number of PVCs per hour, total number of repetitive premature ventricular contractions (PVCs) per hour, and total number of episodes of non-sustained VT. [115] These decreases in VAs were more prominent in patients with ischemic HF compared to patients with idiopathic HF. In contrast, no significant reductions in VAs were noted in the placebo group.

At three months, patients receiving *Coreg* experienced a further reduction in the total number of PVCs per hour, total number of repetitive PVCs per hour, and total number of episodes of non-sustained VT with no significant differences between patients with HF of ischemic or idiopathic origin. [115] No change in the number of VAs was observed among patients in the placebo group. After 6 months, reductions in VAs were sustained in the *Coreg* group while no improvements were noted in the placebo group.

Table 28. Effect of Placebo and *Coreg* on Ventricular Arrhythmias [115]

Parameter	Interval	% Effect on Ischemic HF		% Effect on Idiopathic HF	
		Placebo n = 43	***Coreg*** n = 46	**Placebo** n = 22	***Coreg*** n = 24
PVCt	Baseline	374.7 ± 56	391 ± 63.1	380.6 ± 74.5	374.2 ± 67.5
	1 Month	345.6 ± 86	135.8 ± 43.9*†	356.6 ± 87.4	201.5 ± 84.9*
	3 Months	339.3 ± 91.5	95.3 ± 38.4*‡	360.1 ± 90.8	97.8 ± 33.1*‡
	6 Months	345.3 ± 95.1	90.2 ± 35.4*‡	362.7 ± 91	95.2 ± 30.3*‡
PVCr	Baseline	7.1 ± 3.4	7.6 ± 3	7.8 ± 3.4	6.8 ± 3.3
	1 Month	6.5 ± 3.6	1.8 ± 1.3*†	7.1 ± 3.5	3 ± 2.1*
	3 Months	6 ± 2.2	1 ± 0.6*‡	7.1 ± 3.8	1.1 ± 0.8*‡
	6 Months	5.6 ± 2.2	0.9 ± 0.7*‡	7.4 ± 3.9	0.9 ± 0.7*‡
NSVT	Baseline	12.8 ± 7.4	13.5 ± 7.9	14. 8 ± 9.4	13.6 ± 8.3
	1 Month	12.1 ± 5.9	3.4 ± 3*†	13.2 ± 8.6	5.9 ±3.7*
	3 Months	11.5 ± 6.8	1.3 ± 1.2*‡	12.8 ± 8.7	1.3 ± 1.5*‡

Parameter	Interval	% Effect on Ischemic HF		% Effect on Idiopathic HF	
		Placebo n = 43	*Coreg* n = 46	Placebo n = 22	*Coreg* n = 24
	6 Months	11.3 ± 6.2	1.1 ± 1.0*‡	13.3 ± 9.1	1.5 ± 2.2*‡

HF = heart failure; n = number of patients; PVCt = number of total premature ventricular contractions per hour; PVCr = number of repetitive premature ventricular contractions per hour; NSVT = non-sustained ventricular tachycardia (number of episodes per 24 h).

*$P < 0.05$ compared to baseline; †$P < 0.05$ compared to idiopathic patients treated with carvedilol; ‡$P < 0.05$ compared with 1 month visit.

The most common patient-reported adverse events (> 10%) in the double-blind phase of the *Coreg* and placebo groups, respectively, were as follows: dizziness (30% versus 23%), dyspnea (21% versus 27%), worsening HF (15% versus 20%), diarrhea (14% versus 9%), chest pain (14% versus 16%), bradycardia (12% versus 0%), and hyperglycemia (12% versus 0%). [115]

COMET (*C*arvedilol *O*r *M*etoprolol *E*uropean *T*rial) was a multicenter, double blind, randomized parallel group trial designed to directly compare the effects of *Coreg* and metoprolol tartrate on morbidity and mortality in 3029 patients with NYHA Class II-IV HF. [5] Patients were randomized in a 1:1 fashion to receive either *Coreg* 3.125 mg BID (n = 1511) or metoprolol tartrate 5 mg BID (n = 1518) titrated at two-week intervals to a target dose of *Coreg* 25 mg BID or metoprolol tartrate 50 mg BID.

The addition of *Coreg* for a mean of 58 months to conventional HF therapy was associated with a significant reduction in all-cause mortality compared to metoprolol tartrate. [5] However, the difference between groups in the composite endpoint of all-cause mortality or all-cause hospitalization was not statistically significant. Patients taking *Coreg* had a significantly reduced risk for sudden death as compared to patients taking metoprolol tartrate (8.9% vs 12.1%, $P < 0.05$). Table 29 provides a list of arrhythmic events identified from the serious adverse and adverse events database from COMET.

Table 29. Arrhythmia-Related Adverse Events Reported in COMET[116]

Adverse Event	*Coreg* n = 1,511	Metoprolol Tartrate n = 1,518
Sudden Death	134 (8.9%)*	183 (12.1%)
Ventricular Arrhythmia	13 (0.9%)	24 (1.6%)
Ventricular Tachycardia	55 (3.6%)	58 (3.8%)
Ventricular Fibrillation	27 (1.8%)	25 (1.7%)

n = number of patients.

*$P < 0.5$.

Cice et al also conducted a 6-week, randomized, double-blind, placebo-controlled trial that assessed the effects of Coreg on VAs (Lown Class III-V) in 98 uremic patients maintained on hemodialysis who also had mild to moderate hypertension or CAD [117]. Patients were randomized to receive Coreg 50 mg daily or placebo. Treatment with Coreg significantly reduced the total number of PVCs per hour, total number of repetitive PVCs per hour, and episodes of VT in patients receiving Coreg ($P < 0.001$ for all values versus baseline), while these numbers remained unchanged in the placebo group. No significant adverse events were reported.

Senior et al evaluated the effect of *Coreg* on PVCs in patients with hypertension (group 1, n = 12), stable angina (group 2, n = 41), or HF (group 3, n = 12).[118] Patients in the hypertension and HF groups (groups 1 and 3) received open-label *Coreg* for four and eight weeks, respectively. Patients with angina (group 2) were enrolled into two different protocols. In the first protocol (Group A), there was an initial two-week placebo-phase, followed by the administration of *Coreg* 25 to 50 mg BID for two consecutive weeks; this treatment phase was followed by a second two-week placebo phase. In the second protocol (Group B), following a two week wash-out period, patients were enrolled into a randomized, double-blind, placebo-controlled trial and received either *Coreg* 25 mg BID or matching placebo for four weeks. After the double-blind phase, patients entered into an open-phase trial, in which all patients received *Coreg* 25 mg BID for five months.

An analysis of 24-hour ambulatory electrocardiogram monitoring before and after active therapy with *Coreg* across all 3 groups revealed that 52 of the 65 patients had PVCs.(118) After treatment with *Coreg*, 40 patients (77%) had a reduction in the number of PVCs and 10 patients (20%) had an increase in the number of PVCs. The median number of PVCs per 24 hours decreased from 25.5 to 6.0 ($P < 0.001$) in patients treated with *Coreg*. In 15 patients (23%; n = 65) with multifocal ventricular ectopics, the morphology of the PVC changed from multifocal to unifocal. Non-sustained VT was present in 4 patients, and resolved in all patients after treatment with *Coreg*. Two patients developed non-sustained VT that was asymptomatic; however, QT prolongation was not detected in these patients. R-on-T phenomenon was present in 6 patients before treatment and resolved in 5 patients after treatment with *Coreg*. There was no significant change in the QT interval among patients treated with *Coreg*.

Ventricular Arrhythmias in Post MI Patients with LVD

The CAPRICORN (CArvedilol Post-InfaRct SurvIval COntRol in LV DysfunctioN) trial was a multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the long-term efficacy of *Coreg* in post-MI patients (n = 1959) with LVD, with or without clinical evidence of HF. (6) Patients with a definite myocardical infarction (MI) within the previous 21 days and a left ventricular ejection fraction (LVEF) of ≤ 40% (or wall motion score ≤ 1.3) who were treated with an angiotensin converting enzyme (ACE) inhibitor were randomized to receive either *Coreg* (n = 975) or placebo (n = 984). *Coreg* was initiated at 6.25 mg twice daily (BID), but could be reduced to 3.125 mg BID if not tolerated. *Coreg* was up-titrated at 3 to 10 day intervals to the maximum dose tolerated or 25 mg BID. A retrospective, post-hoc blinded analysis of patient-reported adverse events and serious adverse events in this trial was conducted in order to evaluate the effect of *Coreg* on cardiac arrhythmias.(114) Electrocardiogram confirmation was not available. All events thought to be related to a VA were assigned to one of the following categories: a) ventricular ectopic beats, ventricular tachycardia (VT), ventricular fibrillation (VF), or ventricular flutter and b) "malignant" VAs (i.e. VF and VT only). Analyses were based on time-to-first event.

At the time of randomization, a total of 96 (5%) patients were receiving an antiarrhythmic agent (primarily amiodarone). The comparable rates of VAs in both treatment groups are noted in Table 30.(114)

Table 30. Effects of *Coreg* on Ventricular Arrhythmias in Post-Myocardial Infarction Patients with Left Ventricular Dysfunction(114)

Arrhythmia	*Coreg* n = 975	Placebo n = 984	HR (95% CI)	Log-Rank *P*-Value
All VA	26*	69†	0.37 (0.24-0.58)	< 0.0001
Malignant VA (VF/VT)	9	38	0.24 (0.11-0.49)	< 0.0001

n = number of patients; HR = hazard ratio; CI = confidence interval; VA = ventricular arrhythmias; VF = ventricular fibrillation; VT = ventricular tachycardia.

*Episodes: VF/flutter=4; VT=6: other VAs=19; †Episodes: VF/flutter=17; VT=27; other VAs=38.

A significant reduction in the combined outcomes of death or any VA and death or a malignant VA was reported in patients treated with *Coreg* compared to placebo.(114) The combined outcome of death or any VA was reported in 138 patients treated with *Coreg* compared to 201 patients in the placebo group (HR 0.67, 95% CI 0.54-0.84; $P = 0.0003$). Excluding patients with a history of VT or ventricular flutter, death or any VA was reported in 137 and 197 patients receiving *Coreg* and placebo, respectively (HR 0.68, 95%CI 0.54-0.84; $P = 0.0004$). Death or malignant VA was reported in 123 patients treated with *Coreg* and 173 patients in the placebo group (HR 0.70, 95% CI 0.56-0.89; $P = 0.0028$). Fewer sudden deaths occurred in patients receiving *Coreg* (51 and 69, *Coreg* and placebo, respectively); however, this difference was not statistically significant.

Pre-Marketing Experience

The antiarrhythmic potential of *Coreg* on VAs was evaluated as a secondary endpoint in four randomized, double-blind, placebo-controlled trials using 24-hour Holter monitoring in HF patients already receiving standard HF medications.(119) In two of these studies, patients with NYHA Class II to IV CHF due to ischemic or idiopathic cardiomyopathy received *Coreg* or placebo for three months. The other two studies were part of the U.S. Phase III clinical trials program; one of these trials evaluated patients receiving either *Coreg* or placebo for 6 months in patients with mild to moderate HF, while the other study evaluated the

effects of 6 months of *Coreg* compared to placebo in patients with severe CHF (NYHA Classes III and IV). This latter trial was terminated early after a significant reduction in morbidity and mortality was observed in the cumulative U.S. Carvedilol HF trials. Thus, only a small number of patients completed the double-blind phase, and almost all comparisons in this study were under-powered for statistical analysis.

Holter monitoring data were analyzed at baseline and at the end of each study.[119] There was a wide variability in the parameter values observed in each trial. Treatment with *Coreg* tended to decrease the incidence of PVCs per hour, number of paired PVCs per day, and episodes of VT (Table 31).

A meta-analysis of the Holter monitor data from these four studies showed a statistically significant difference in mean change from baseline for *Coreg* versus placebo for the number of paired PVCs per 24 hours ($P = 0.024$) and VT events per 24 hours ($P = 0.006$).[119]

Table 31. The Effect of Chronic Therapy with *Coreg* vs. Placebo on Continuous Electrocardiographic Recordings (Holter Monitoring) - Change from Baseline Values*[119]

Study #	Change in Mean PVCs/hr		Change in VT Events/day		Change in # Runs of Longest VT Events(beats)	
	Coreg	**Placebo**	***Coreg***	**Placebo**	***Coreg***	**Placebo**
033	n = 32	n = 20	n = 32	n = 18	n = 13	n = 9
	-104.53 ± 284.78	-43.10 ± 126.84	57.2 ± 154.4	5.1 ± 13.0	-5.0 ± 19.3	-0.8 ± 2.5
035	n = 26	n = 11	n = 25	n = 11	n = 25	n = 11
	-8.48 ± 302.86	161.05 ±223.4	-6.7 ± 110.4	12.4 ± 41.0	-0.8 ± 6.0	2.2 ± 4.1
221*	n = 95	n = 97	n = 93	n = 91	n = 95	n = 97
	-54.66 ± 232.94	-40.96 ± 236.17	-22.09 ± 117.70	4.05 ± 149.70	-0.66 ± 5.4	-0.31 ± 7.1
239*	n = 16	n = 5	n = 15	n = 5	n = 16	n = 5
	-77.06 ± 220.73	-28.78 ± 115.10	-40.75 ± 152.73	-5.36 ± 12.05	-2.3 ± 4.3	-1.4 ± 1.9

n = number of patients; PVC = premature ventricular contraction; VT = ventricular tachycardia.

*Data reported as change from baseline in mean values, (mean ± SD); statistical evaluation of mean change from baseline within each group not done.

6. OUTCOME AND ECONOMIC EVALUATION

6.1 Outcome and Economic Data for Carvedilol

6.2 The Effect of Dosage and Adherence to Hospitalizations and Costs

Effect of dosage and adherence to carvedilol on hospitalizations in hypertension, heart failure, and post-MI patients

The association between the dosage of therapy with carvedilol, adherence with such therapy, and hospitalizations and healthcare costs was assessed in a longitudinal observational study in patients with hypertension, heart failure, and patients post-MI.[120] Study subjects consisted of all persons > 18 years of age in a large multi-plan managed care database with two or more outpatient pharmacy claims for carvedilol between January 1, 2000 and December 31, 2004. The date of each patient's first claim for carvedilol during this period was designated the "index date". Patients with less than 12 months of complete medical and pharmacy claims data prior to their index date or less than 12 months of follow-up claim data were excluded. Patients were also excluded if they did not have two or more outpatient claims or one or more inpatient claims with a diagnosis of heart failure, myocardial infarction, or hypertension on or before their index date. Additionally, patients greater than 65 years of age not enrolled in a Medicare risk-sharing plan were excluded due to incomplete medical and pharmacy data. The follow-up period for each patient began with the index date and ended with the last date of continuous claims history. Follow-up was truncated with discontinuation of carvedilol therapy (continuous period of > 180 days without any days supplied of carvedilol) or receipt of a beta-blocker other than carvedilol.

For each patient, follow-up was partitioned into fixed 90-day intervals beginning with the index date and carvedilol dosage and adherence were assessed on a quarterly basis.[120] The daily dosage of carvedilol was calculated as the average daily dose for all days of carvedilol therapy received during each quarter. Adherence represents the medication possession ratio (days for which the patient was supplied carvedilol divided by the number of days of follow-up). The primary analyses assessed the relationship between outcome in each quarter and mean adherence and dosage over all the prior quarters, including the quarter with the observed outcomes.

A total of 7,952 patients followed for a mean of 10.8 ± 6.2 months were included in the analysis.[120] The mean age was 57 ± 12 years and 62% of patients were male. In the period 12 months prior to patients' respective index dates, the Charlson comorbidity index was 2.1 ± 2.0 and documentation for heart failure, MI, hypertension, or other cardiovascular (CV) disease was noted in 53%, 19%, 81%, and 60% of patients, respectively. Patients received a mean of 39 ± 36 prescriptions during those 12 months, including the following: ACE inhibitors (56%), angiotensin II receptor blockers (ARBs) (22%), beta-blockers (35%), calcium channel blockers (25%), diuretics (50%), digoxin (4%), diabetes medications (29%), lipid-lowering medications (43%), anticoagulants (14%). Patients experienced a mean of 0.64 ± 1.00 CV-related hospitalizations and 0.13 ± 0.46 hospitalizations for non-CV reasons. Mean CV-related and non-CV-related costs per patient over the 12 months totaled $13,793 ± $31,178 and $11,261 ± $33,130, respectively.

Results

Unadjusted rates for CV-related and all-cause hospitalizations for dosage ranges and adherence rates are presented in Table 32.[120] There was an inverse relationship between the mean daily dose of carvedilol and adherence rates and both CV-related and all-cause hospitalization.

Table 32. Outcomes (Per Quarter) by Daily Dosage and Adherence Categories[120]

Adherence	Dosage for Carvedilol < 12.5 mg	Dosage for Carvedilol 12.5 to < 25 mg	Dosage for Carvedilol 25 to < 50 mg	Dosage for Carvedilol 50 mg
Cardiovascular-Related Hospitalizations, Number (% per quarter)				
< 50%	114 (11.9)	86 (8.4)	57 (7.7)	46 (4.3)
50% to < 80%	116 (10.6)	150 (7.8)	122 (8.0)	94 (5.4)
80% to < 100%	180 (9.9)	182 (5.9)	172 (6.1)	148 (4.1)
100%	170 (7.8)	175 (5.1)	109 (3.9)	129 (3.1)
All-Cause Hospitalizations, Number (% per quarter)				
< 50%	146 (15.3)	115 (11.2)	74 (10.0)	65 (6.1)
50% to < 80%	153 (13.9)	197 (10.3)	151 (10.0)	128 (7.4)
80% to < 100%	230 (12.6)	260 (8.4)	220 (7.8)	207 (5.7)
100%	224 (10.3)	221 (6.4)	147 (5.3)	192 (4.5)

When dosage and adherence were analyzed as continuous variables and adjusted for all baseline characteristics, there was an 8% risk reduction in CV-related hospitalizations for every 10% increase in adherence (95% Confidence Interval [CI] 6-11%, $P < 0.001$) and a 10% risk reduction in CV-related hospitalizations for every 10 mg increase in dose (95% CI 6-13%, $P < 0.001$).[120] For all-cause hospitalizations, there was an 8% risk reduction for every 10% increase in adherence (95% CI 6-10%, $P < 0.001$) and 9% risk reduction for every 10 mg increase in dose (95% CI 6-12%, $P < 0.001$). There was a trend towards a reduction in total (inpatient, outpatient, and pharmacy) CV-related and all-cause costs with increasing mean daily doses of carvedilol and improved adherence rates. Patients taking carvedilol 50 mg daily had a 32% lower CV-related ($P = 0.005$) and 22% lower all-cause ($P < 0.001$) costs than those patients taking doses < 12.5 mg. Patients who were 100% adherent to therapy with carvedilol also had a 17% reduction in all-cause costs compared to those who were < 50% adherent ($P = 0.014$). At one year, there was an observed reduction in CV-related costs of 3% and 3% (P = NS), respectively, and all-cause costs of 2% ($P = 0.01$) and 3% (P = NS), respectively with every 10% improvement in adherence and 10 mg increase in dose. Increases in outpatient pharmacy costs related to improvements in adherence, were offset due to a reduction in hospitalizations and associated costs.

Effect of Dosage and Adherence to Carvedilol on Hospitalizations in Patients with Heart Failure and in Patients Post-Myocardial Infarction

All analyses were repeated for a subgroup of 4780 patients (mean age 58 ± 13 years) with heart failure and/or myocardial infarction, who were followed for a mean duration of 11.0 ± 6.3 months.[120] In this subgroup 89% of patients had a history of heart failure, 31% had a myocardial infarction, 68% had hypertension, and 72% had other CV diseases documented in the 12 months prior to the their index prescription for carvedilol. Within those 12 months, patients had a mean of 41 ± 37 prescriptions filled, a mean number of 0.94 ± 1.14 CV-related hospitalizations and incurred mean CV-related costs of $19,888 ± 37,145 per patient. Adjusted risks for CV-related and all-cause hospitalizations as determined by rates of adherence and mean daily doses of carvedilol are presented in Table 33.

Table 33. Adjusted Risks for CV-Related and All-Cause Hospitalizations by Daily Dosage and Adherence Categories[120]

CV-Related Hospitalizations			
Adherence	**Odds Ratio (95% CI)**	**Total Daily Mean Dose**	**Odds Ratio (95% CI)**
< 50%	1.00 (Referent)	< 12.5 mg	1.00 (Referent)
50% to < 80%	0.75 (0.61-0.93)*	12.5 mg to < 25 mg	0.75 (0.65-0.87)†
80% to < 100%	0.58 (0.47-0.72)†	25 mg to < 50 mg	0.75 (0.63-0.88)†
100%	0.55 (0.43-0.69)†	50 mg	0.50 (0.41-0.62)†
All-Cause Hospitalizations			
< 50%	1.00 (Referent)	< 12.5 mg	1.00 (Referent)
50% to < 80%	0.75 (0.61-0.91)‡	12.5 mg to < 25 mg	0.76 (0.66-0.87)†
80% to < 100%	0.59 (0.49-0.72)†	25 mg to < 50 mg	0.73 (0.63-0.85)†
100%	0.55 (0.44-0.69)†	50 mg	0.54 (0.45-0.65)†
CI = confidence interval; CV = cardiovascular; **P*-value = 0.008; †*P*-value < 0.001; ‡*P*-value = 0.004			

For every 10% increase in adherence to carvedilol therapy for patients with heart failure and/or MI, there was a 9% risk reduction in CV-related and all-cause hospitalizations (95% CI 7-12%, $P < 0.001$ for both parameters).[120] In addition, every 10% increase in adherence led to a decrease in CV-related costs by 6% (95% CI 2-10%, $P = 0.005$) and all-cause costs by 4% (95% CI 2-6%, $P = 0.001$). For every 10 mg daily dose increase of carvedilol, an 11% risk reduction in CV-related (95% CI 7-15%, $P < 0.001$) and a 10% risk reduction in all-cause hospitalizations (95% CI 7-14%, $P < 0.001$) was seen. These risk reductions translated into incremental CV-related cost reductions of 6% (95% CI 0-12%, $P = 0.036$) and all-cause cost reductions of 4% (95% CI 0-7%, $P = 0.051$).

6.3 Clinical Value and Overall Costs

Beta-blocker therapy is recommended for all patients with stable heart failure (HF) due to left ventricular dysfunction (LVD) unless otherwise contraindicated.[18] Currently only *Coreg CR*, *Coreg*, and metoprolol CR/XL have indications for HF. *Coreg CR* and *Coreg* are the only beta-blockers proven effective in reducing mortality in patients with severe HF and for patients who have survived the acute phase of a myocardial infarction (MI) and have LVD. *Coreg CR* and *Coreg* are also indicated for the management of hypertension. The 2006 American Association of Clinical Endocrinologists (AACE) Hypertension Guidelines differentiate beta-blockers, noting that drugs (such as carvedilol) that block both alpha- and beta-receptors may prove particularly beneficial for the treatment of hypertension in patients with diabetes, because they cause vasodilation and an increase in insulin sensitivity.[52] Several clinical benefits complemented by a favorable economic profile make *Coreg CR* an evidence-based choice for formulary inclusion. These clinical features and benefits include:

- *Coreg CR* has demonstrated pharmacokinetic and predicted pharmacodynamic equivalence to *Coreg* in patients with HF and post-MI LVD.[76]
- *Coreg* reduced all-cause mortality by 65% ($P < 0.0001$) in patients with mild-to-moderate HF and 35% in patients with severe HF ($P = 0.001$) compared to placebo[2] [3]
- In patients with mild-to-moderate HF, *Coreg* reduced the risk of all-cause hospitalizations by 29% ($P = 0.009$), cardiovascular hospitalizations by 28% ($P = 0.041$), and HF hospitalizations by 38% ($P =$

0.041) compared to placebo. Therapy with *Coreg* also shortened the number of days in hospital per patient from 3.08 days to 1.56 days for cardiovascular hospitalizations ($P = 0.019$) and from 1.67 days to 0.54 days for HF hospitalizations ($P = 0.025$)[121]

- In patients with severe heart failure, therapy with *Coreg* compared to placebo resulted in 20% fewer hospitalizations for any reason ($P = 0.002$), 28% fewer hospitalizations for cardiovascular reasons ($P = 0.0002$), and 33% fewer hospitalizations for HF ($P < 0.0001$). Patients receiving *Coreg* spent 27% fewer days in the hospital for any reason (6.2 versus 8.5 days per patient, $P = 0.0005$) and 40% fewer days in the hospital for HF (2.9 versus 4.9 days per patient, $P < 0.0001$) [4]
- In a head-to-head mortality trial comparing *Coreg* to metoprolol tartrate in New York Heart Association (NYHA) Class II-IV HF, therapy with *Coreg* compared to metoprolol tartrate significantly reduced the risk of all-cause mortality by 17% ($P = 0.017$), reduced the risk of cardiovascular death by 20% ($P = 0.0004$), reduced the risk for sudden death by 19% ($P = 0.02$), and reduced the risk of fatal or nonfatal MI by 30% ($P = 0.04$) [5] [122]
- In post-MI patients with LVD, therapy with *Coreg*, in addition to current standard therapies, including ACE inhibitors, reduced the risk of all-cause mortality by 23% ($P = 0.03$), cardiovascular mortality by 25% ($P = 0.024$), and fatal or nonfatal myocardial infarction by 40% ($P = 0.01$) compared to standard therapy alone [6,55]
- In patients with essential hypertension, therapy with *Coreg CR* 20, 40, and 80 mg resulted in significant and dose-dependent reductions in mean 24 hour systolic and diastolic blood pressures (BP) measured by ambulatory BP monitoring[90]
- In a head-to-head trial comparing *Coreg* to metoprolol tartrate in patients with mild to moderate hypertension and type 2 diabetes mellitus (DM), *Coreg* (mean dose 35 mg daily) compared to metoprolol tartrate (mean dose 256 mg daily) demonstrated equivalent blood pressure control without adversely affecting metabolic or cardiovascular risk factors. Metoprolol tartrate increased HbA_{1c} (change from baseline to endpoint: +0.15%, $P < 0.001$), while *Coreg* did not have an effect on HbA_{1c} (+0.02%, $P = 0.65$), resulting in a 0.13% difference in the change in HbA_{1c} from baseline in favor of *Coreg* ($P = 0.004$). Insulin sensitivity (Homeostatic Model Assessment-Insulin Resistance [HOMA-IR]) improved with *Coreg* (-9.1%, $P = 0.004$) and therapy with *Coreg* also reduced patients' albumin/creatinine ratio by 14% from baseline[7]

Cost Justification

Therapy with *Coreg* has been demonstrated to significantly reduce the risk for mortality and hospitalizations in patients with heart failure (HF) and left ventricular dysfunction (LVD) following a myocardial infarction (MI). [4] [6] By reducing the risk of hospitalizations, *Coreg* has been shown to have the additional benefit of reducing resource utilization.[121]

In a recent observational study using a large managed care claims dataset, the relationship between adherence to *Coreg*, dosage of therapy, and costs was evaluated.[120] The analysis of hypertensive, HF, and/or post-MI patients taking *Coreg* demonstrated that for each 10% improvement in adherence to *Coreg*, there was a 8% reduction in the risk of a cardiovascular (CV)- related or all-cause hospitalization. This decrease in hospital risk translated into 3% and 2% reductions in CV-related and all-cause healthcare costs, respectively. There was a similar independent risk and cost reduction for every 10 mg increase in *Coreg* dose. In patients with HF and/or post-MI only, the risk reduction for CV-related and all-cause hospitalizations was 9% for every 10% improvement in adherence. This translated into cost savings of 6% for CV-related costs and 4% for all-cause healthcare costs. In addition, a similar independent risk and cost reduction was observed with every 10 mg increase in dose. This suggests that CV-related and all-cause costs can be reduced among patients taking *Coreg* by improving adherence by at least 10% and increasing the tolerated dose by at least 10 mg per day.

A budget impact economic model was developed to assess the Per Member Per Month (PMPM) cost impact of switching patients from *Coreg* to *Coreg CR*.[123] The impact model incorporates the adherence data on *Coreg* above and a cost analysis of patients that switched from a twice daily beta-blocker to a once daily beta-blocker among a cohort of patients with CV disease.[123,124] In the switching analysis, patients were followed for at least 6 months pre- and post-switch looking at costs and utilizations over those defined observation periods.

Switching 50% of patients receiving *Coreg* to *Coreg CR*, resulted in a reduction in PMPM costs of $0.02. [123] Drug acquisition cost was increased about 7.8% due to higher adherence with *Coreg CR*, but this was offset by a subsequent decrease in inpatient costs due to fewer inpatient visits observed with patients taking *Coreg CR* (due to improved adherence), as well as fewer outpatient visits observed in the switching analysis study for those patients who were switched from a twice daily regimen to a once daily regimen. The budget impact model is sensitive to changes in adherence rates, acquisition costs, risk reduction assumptions, and switch rates. Further cost savings could be observed by increasing the percent of patients switched from *Coreg* to *Coreg CR*, having a lower acquisition price for *Coreg CR*, or by increasing the adherence difference by more than 10%, which would result in a greater risk reduction in hospitalizations and related cost of care.

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Appendix

Table 19. Pharmacologic and Pharmacokinetic Properties of Beta-Adrenergic Blocking Agents[80,81,82,83,84]

Generic Brand	Indications for Use	Oral Dosage Strengths	Usual Daily Dose	Site of Effect	ISA	MSA	Lipophilicity	Absolute Oral Bioavailability (%)	Protein Binding (%)	Metabolism	Half-life (hours)	Elimination (%) Unchanged
Acebutolol Sectral®	HTN PVCs	200, 400 mg capsules	HTN: 400-800 mg/day PVCs: 400-1200 mg/day	β-1†	+	+	low	40	26	Hepatic	3-4	Renal (30-40)
Atenolol Tenormin®	HTN Angina MI	25, 50, 100 mg tablets	50-100 mg/day	β-1†	0	0	low	50-60	6-16	Little or no hepatic	6-7	Renal (50)
Betaxolol Kerlone®	HTN	10, 20 mg tablets	10-20 mg/day	β-1†	0	+	low	89	»50	Hepatic	14-22	Renal (15)
Bisoprolol Zebeta®	HTN	5, 10 mg tablets	5-20 mg/day	β-1†	0	0	low	80	»30	Hepatic	9-12	Renal (50) <2% Fecal
Carvedilol/ Carvedilol phosphate Coreg®/ Coreg CR™	Mild-Severe HF Post-MI LVD HTN	Carvedilol: 3.125, 6.25, 12.5 and 25 mg tablets Carvedilol phosphate: 10, 20, 40, 80 mg capsules	Carvedilol: 3.125-25 mg BID Carvedilol phosphate: 10-80 mg QD	β-1 β-2 a-1	0	0	high	Carvedilol: 25-35 Carvedilol phosphate: 21-30	98	Hepatic	Carvedilol: 7-10 Carvedilol phosphate enantiomers: 10.4 (R+) 11.5 (S-)	Renal (<2)

BID = twice daily; HF = heart failure; HTN = hypertension; IR = immediate release; ISA = intrinsic sympathomimetic activity; IV = intravenous MI = myocardial infarction; Mod = moderate; MSA = membrane stabilizing activity; NA = not applicable; QD = once daily; PVC = premature ventricular contractions; RBC = red blood cell; SR = sustained release.

*Dose for hypertension unless noted; †Inhibits β-2 receptors at higher doses; ‡Not applicable because only available as an intravenous preparation; §Only the immediate release form of metoprolol (metoprolol tartrate); ¶Only the extended release form of metoprolol (metoprolol succinate); #Betapace AF® is only indicated for atrial fibrillation/flutter; **240 mg only available for Betapace® formulation; ††Inhibits β-2 receptors in poor metabolizers and at higher doses; ‡‡Half life is dependent upon whether the patient is an extensive or poor metabolizer.

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Esmolol Brevibloc®	Supra-ventricular, noncompensatory sinus, and intra- & postoperative tachycardia	IV only	NA‡	β-1†	0	0	low	N/A	55	Esterase in cytosol of RBCs	0.15	Renal (<2)
Labetalol Normodyne®/ Trandate®	HTN	100, 200, 300 mg tablets	200-800 mg /day	β-1 β-2 α-1	0	0	moderate	25	»50	Hepatic	6-8 (po)	Renal (55-60); Biliary/ fecal
Metoprolol Tartrate/ Metoprolol Succinate Lopressor®/ Toprol XL®	HTN Angina MI§ Mild-Mod. HF¶	Metoprolol Tartrate: 25, 50, 100 mg tablets Metoprolol Succinate: 25, 50, 100, 200 mg tablets	Metoprolol Tartrate: 100-450 mg/day Metoprolol Succinate: 25-200 mg/day	β-1†	0	0	moderate	40-50/ 77	12	Hepatic	3-7	Renal (<5)
Nadolol Corgard®	HTN Angina	20,40,80,120, 160 mg	40-240 mg/day	β-1 β-2	0	0	low	»30	30	None	20-24	Renal (100)
Nebivolol Bystolic™	HTN	2.5, 5, 10 mg	5-40 mg/day	β-1††	0	0	high	12% in extensive metabolizers; 96% in poor metabolizers	98	Hepatic	Nebivolol enantiomer (d-nebivolol): 12-19‡‡	Renal and Fecal (<0.5)

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Penbutolol Levatol®	HTN	20 mg	20-80 mg/day	β-1 β-2	+	0	high	»100	80-98	Hepatic	»5	Renal
Pindolol Visken®	HTN	5, 10 mg tablets	5-60 mg/day	β-1 β-2	+++	0	low	>95%	40	Hepatic	3-4	Renal (35-40)
Propranolol/ Propranolol SR Inderal® /Inderal LA®	IR & SR: HTN Angina Migraine Prophylaxis Hyper-trophic subaortic stenosis IR only: MI Arrythmias Essential Tremor Pheochromo-cytoma	10, 20, 40, 60, 80 mg IR 60, 80, 120, 160 mg SR	40-320 mg/day	β-1 β-2	0	++	high	30/9-18	90	Hepatic	4-10	Renal (<1)
Sotalol Betapace®/ Betapace AF®	Ventricular Arrhythmia/ Tachycardia Atrial Fibrillation/ Flutter#	Sotalol: 80, 120, 160, 240** mg tablets	160-320 mg/day	β-1 β-2	0	0	low	90-100	0	Not metabolized	12	Renal (100)
Timolol Blocadren®	HTN MI Migraine	5, 10, 20 mg	10-60 mg/day	β-1 β-2	0	0	low-to-moderate	»90	<10%	Hepatic	4	Renal

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